

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
31 January 2002 (31.01.2002)

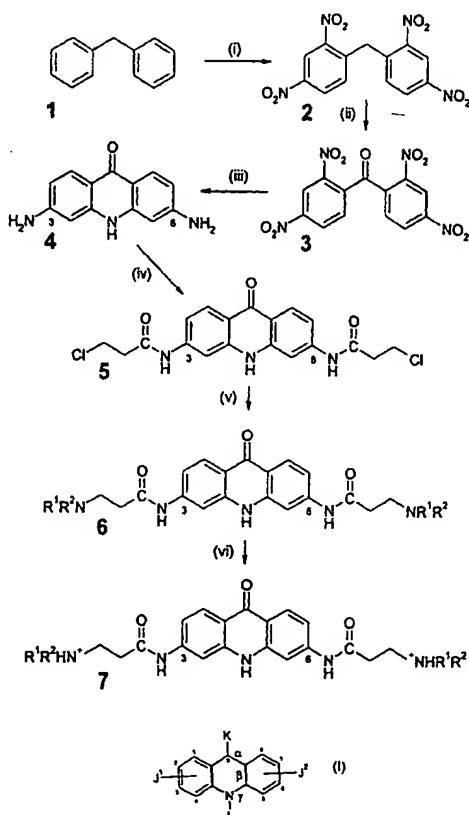
PCT

(10) International Publication Number
WO 02/08193 A2

- (51) International Patent Classification⁷: C07D 219/00
- (21) International Application Number: PCT/GB01/03046
- (22) International Filing Date: 6 July 2001 (06.07.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/216,624 7 July 2000 (07.07.2000) US
- (71) Applicant (for all designated States except US): CANCER RESEARCH VENTURES LIMITED [GB/GB]; Cambridge House, 6-10 Cambridge Terrace, Regent's Park, London, Greater London NW1 4JL (GB).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): NEIDLE, Stephen [GB/GB]; Rainbow's End, Rainbow Court, Oxhey, Hertfordshire WD1 4RP (GB). HARRISON, Richard, John [GB/GB]; 58 Blenheim Gardens, Reading, Berkshire RG1 5QG (GB). KELLAND, Lloyd, Royston [GB/GB]; 123 Hitchings Way, Reigate, Surrey RH2 8EP (GB). GOWAN, Sharon, Michele [GB/GB]; 26 Meadway, Tolworth, Surrey KT5 9RG (GB). READ, Martin [GB/GB]; 2 Granfield Street, Battersea, London, Greater London SW11 3JH (GB). RESZKA, Tony [GB/GB]; 151 Victoria Street, Kilburn, London, Greater London NW6 6DE (GB).
- (74) Agents: ARMITAGE, Ian, A. et al.; Mewburn Ellis, York House, 23 Kingsway, London, Greater London WC2B 6HP (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,

[Continued on next page]

(54) Title: THERAPEUTIC ACRIDONE AND ACRIDINE COMPOUNDS



(57) Abstract: The present invention pertains to acridone and acridine compounds of formula (I), wherein either: (a) K is =O, L is -H, alpha is a single bond, beta is a double bond, gamma is a single bond (acridones); or, (b) K is a 9-substituent, L is absent, alpha is a double bond, beta is a single bond, gamma is a double bond (acridines); and wherein: J¹ is a 2- or 3-substituent; J² is a 6- or 7-substituent; J¹ and J² are each independently a group of the formula -NHCO(CH₂)_nNR¹R², wherein: n is an integer from 1 to 5; and, R¹ and R² are independently hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl, or R¹ and R², taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 3 to 8 ring atoms; and wherein, when K is a 9-substituent, K is a group of the formula -N(R^N)Q, wherein: R^N is an amino substituent and is hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl; and, Q is C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl, and is optionally substituted; and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit telomerase, to regulate cell proliferation, and in the treatment of proliferative conditions, such as cancer.



DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

- (84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- without international search report and to be republished upon receipt of that report
- entirely in electronic form (except for this front page) and available upon request from the International Bureau

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

THERAPEUTIC ACRIDONE AND ACRIDINE COMPOUNDS

RELATED APPLICATION

5

This application claims priority to United States provisional patent application no. 60/216,624 filed 07 July 2001, the contents of which are incorporated herein by reference in their entirety.

10

TECHNICAL FIELD

This invention pertains generally to the field of telomerase inhibitors and antiproliferative agents, and more specifically to certain acridone and acridine compounds which inhibit telomerase and/or regulate cell proliferation. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit telomerase, to regulate cell proliferation, and in the treatment of proliferative conditions, such as cancer.

20

BACKGROUND

Mammalian cells are normally subject to tight controls regulating replication in order to maintain organ structure and function. Conversely, the disease of cancer is characterized by uncontrolled proliferation. Compromise of any of the steps involved in cell cycle regulation could be involved in escape from regulatory mechanisms and therefore lead to neoplasia. However, even if a cell escapes proliferation suppression, there are limitations to the number of replicative cycles it can progress through before safety mechanisms cause cell cycle shutdown, and this restriction is thought to be a component of the process of organismal aging. Although aging is a complex process, a major candidate for the molecular signal for replicative senescence is that of telomere shortening.

- 2 -

Telomeres are nucleoprotein structures at the ends of linear chromosomes consisting of DNA sequences arranged in tandemly repeated units which extend from less than 100 to several thousands of bases. In contrast to chromosome ends created by random breakage, telomeres are stable structures not prone to
5 degradation or fusion with other chromosome ends and are not subject to DNA repair mechanisms.

During each round of cellular replication, both strands of DNA separate and daughter strands are synthesized in a slightly different manner on the leading and
10 lagging strand. While the lead strand replicates in a continuous fashion using conventional DNA polymerase, the lagging strand replicates in a discontinuous fashion using Okazaki fragments. The gaps between individual Okazaki fragments are filled by the regular DNA polymerase. However, this sets the stage for a potential "end replication problem." This arises because Okazaki fragment priming
15 will not necessarily start at the very end of the DNA and because the RNA primer, once removed, would result in a portion of unreplicated 3'-DNA (an unrepaired 3'-overhang). This can lead to a loss of 50-200 base pairs with every round of somatic cell division, with eventual shortening of telomeres to a length that coincides with the activation of an antiproliferative mechanism termed "mortality
20 stage 1" (M1), and at this stage, senescence in somatic cells occurs. Thus, telomere shortening functions as a "mitotic clock" and limits division in somatic cells to about 50-70 times, thereby contributing to cell aging.

In some cells, due to various mechanisms, the M1 stage is bypassed and cells can
25 continue to divide until telomeres become critically shortened ("mortality stage 2," M2). At this M2 stage, in many immortalized cells, a specialized DNA polymerase called "telomerase" appears and utilizes its internal RNA template to synthesize the telomeric sequence and compensate for the loss of telomeric DNA due to incomplete replication. This prevents further shortening of telomeres, and the
30 resulting stabilization of their length contributes to immortalization.

Telomerase is not expressed, or if it is, its activity is repressed, in most normal mammalian somatic cells. Exceptions to this rule include male germ line cells and

- 3 -

some epithelial stem cells (e.g., as in the intestinal crypts, the basal layer of the epidermis, and within human hair follicles).

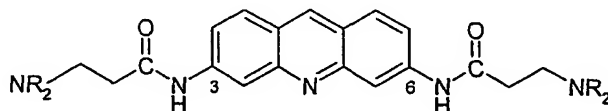
Nonetheless, both telomerase activity and shortened but stabilized telomeres have been detected in the majority of tumours examined (and in over 90% of all human
5 cancers examined), and consequently, telomeres and telomerase are recognized targets for anti-neoplastic (e.g., cancer) chemotherapy.

The absence of telomerase in most normal cells makes this enzyme a particularly attractive target, considering that its inhibition would probably cause minimal
10 damage to the whole patient. The fact that tumour cells have shorter telomeres and higher proliferation rates than normal replicative cell populations suggests that a therapeutic telomerase inhibitor may cause tumour cell death well before damage to regenerative tissues occurs, thereby minimizing undesirable side-effects.

15 For a more detailed discussion of telomeres and telomerase, and their role as anti-proliferative targets, see, for example, Sharma et al., 1997; Urquidi et al., 1998; Perry et al., 1998c; Autexier, 1999; and Neidle et al., 1999, and references therein.

A number of polycyclic compounds, including polycyclic acridines, anthraquinones,
20 and fluorenones have been shown to inhibit telomerase and/or to have anti-tumour effects *in vitro*. See, for example, Bostock-Smith et al., 1999; Gimenez-Arnau et al., 1998; Gimenez-Arnau et al., 1998; Hagan et al., 1997; Hagan et al., 1998; Harrison et al., 1999; Julino et al., 1998; Perry et al., 1998a, 1998b, 1999a, 1999b; Sun et al., 1997.

25 Harrison et al., 1999, describe certain 3,6-disubstituted acridines which are shown to inhibit telomerase, and to inhibit cell growth in certain ovarian carcinoma cell lines.



- 4 -

Read et al., April 2001, describe certain 3,6,9-trisubstituted acridines (see compounds 3 and 4 in Figure 1 therein), including **BR-ACO-19** and **BR-ACO-20** which are shown to have potent in vitro inhibitory activity against human telomerase.

5

Although many are known, there remains a great need for potent telomerase inhibitors and antitumour agents, particularly for such compounds which offer additional pharmacological advantages. For example, particularly preferred telomerase inhibitors are ones which are characterized by one or more of the

10 following properties:

(a) no inhibition of *Taq* polymerase at 10-50 μ M (in order to provide specificity and eliminate broad-spectrum polymerase inhibitors);

(b) cell free telomerase inhibition (at <1 μ M) at concentrations more than 5 to 10-fold less than for concentrations for acute cytotoxicity;

15 (c) shortening of telomere length in tumour cells at concentrations 5 to 10-fold less than concentrations for acute cytotoxicity;

(d) telomere shortening in human tumour xenografts; and,

(e) oral bioavailability.

20

SUMMARY OF THE INVENTION

One aspect of the invention pertains to active compounds as described herein.

25 Another aspect of the invention pertains to a composition comprising an active compound as described herein and a pharmaceutically acceptable carrier or diluent.

Another aspect of the invention pertains to an active compound as described herein for use in a method of treatment of the human or animal body.

30

Another aspect of the invention pertains to use of an active compound as described herein for the manufacture of a medicament for use in the treatment of a proliferative condition.

- 5 -

Another aspect of the invention pertains to a method of inhibiting telomerase *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of an active compound as described herein.

5

Another aspect of the invention pertains to a method of regulating cell proliferation, *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of an active compound as described herein.

10 Another aspect of the invention pertains to a method for the treatment of a proliferative condition comprising administering to a subject suffering from said proliferative condition a therapeutically-effective amount of an active compound as described herein.

15 As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspect of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

20 Figure 1 is a scheme illustrating a chemical synthesis method for certain 3,6-disubstituted acridones of the present invention.

Figure 2 is a scheme illustrating a chemical synthesis method for certain 2,7-disubstituted acridones of the present invention.

25

Figure 3A is a scheme illustrating a chemical synthesis method for certain 2,6-disubstituted acridones of the present invention.

30 Figure 3B is another scheme illustrating a chemical synthesis method for certain 2,6-disubstituted acridones of the present invention.

Figure 4 is a scheme illustrating a chemical synthesis method for certain 3,6,9-trisubstituted acridines of the present invention.

- 6 -

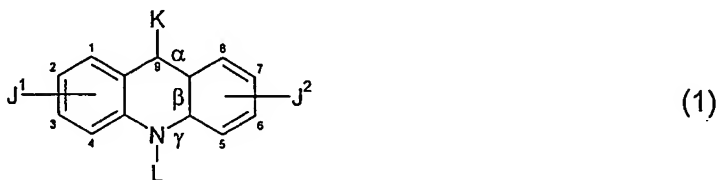
Figure 5 is a scheme illustrating a chemical synthesis method for certain 2,7,9-trisubstituted acridines of the present invention.

- 5 Figure 6 is a scheme illustrating a chemical synthesis method for certain 2,6,9-trisubstituted acridines of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

10 Compounds

The present invention pertains generally to a class of compounds referred to herein as "acridones" and "acridines" which have the following general formula:



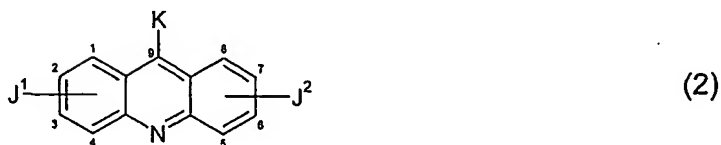
wherein either:

- 15 (a) K is =O, L is -H, α is a single bond, β is a double bond, γ is a single bond (i.e., "acridones"); or,
- (b) K is a 9-substituent, L is absent, α is a double bond, β is a single bond, γ is a double bond (i.e., "acridines"); and,
- J¹ is a 2- or 3-substituent; and,
- 20 J² is a 6- or 7-substituent;
- and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

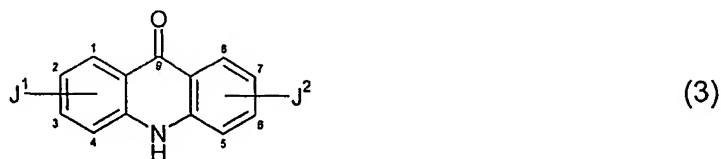
- As will be appreciated by the skilled artisan, the above structure is one of many possible resonance structures which may be drawn to depict the same compound.
- 25 As used herein, a reference to one such structure is to be considered a reference to all possible corresponding resonance structures.

- 7 -

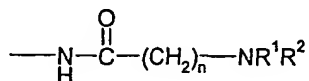
Thus, in one embodiment, the compounds are "acridines" of the following formula:



In another embodiment, the compounds are "acridones" of the following formula:



- 5 In one preferred embodiment, whether acridine or acridone, J^1 is a 2-substituent and J^2 is a 6-substituent (i.e., 2,6-disubstituted). In one preferred embodiment, J^1 is a 3-substituent and J^2 is a 7-substituent (i.e., 3,7-disubstituted). These embodiments may conveniently be referred to as "symmetrical" compounds.
- 10 In one preferred embodiment, whether acridine or acridone, J^1 is a 2-substituent and J^2 is a 7-substituent (i.e., 2,7-disubstituted), or, equivalently, J^1 is a 3-substituent and J^2 is a 6-substituent (i.e., 3,6-disubstituted). These embodiments may conveniently be referred to as "non-symmetrical" compounds.
- 15 In the compounds of the present invention, J^1 and J^2 are each independently a group of the formula:



wherein n is an integer from 1 to 5, and $\text{---NR}^1\text{R}^2$ is a terminal amino group.

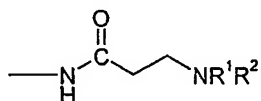
- 20 In one preferred embodiment, n is an integer from 1 to 4.
In one preferred embodiment, n is an integer from 1 to 3.
In one preferred embodiment, n is 1 or 2.
In one preferred embodiment, n is 1.
In one preferred embodiment, n is 2.
- 25 In one preferred embodiment, n is 3.

- 8 -

In one preferred embodiment, n is 4.

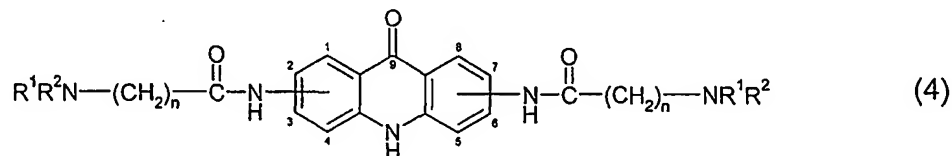
In one preferred embodiment, n is 5.

- In one preferred embodiment, n is 2, and J¹ and J² are each independently a group
 5 of the following formula, wherein -NR¹R² is a terminal amino group:

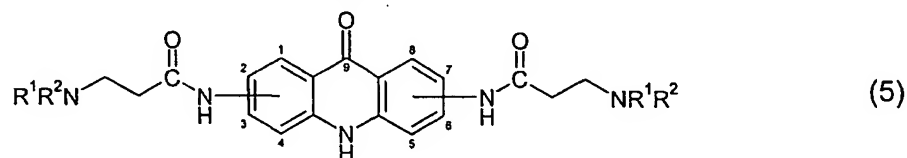


In one preferred embodiment, J¹ and J² are the same.

- 10 Thus, in one embodiment, the compounds are acridones, and have the following formula, wherein n is as defined above, and -NR¹R² is a terminal amino group:

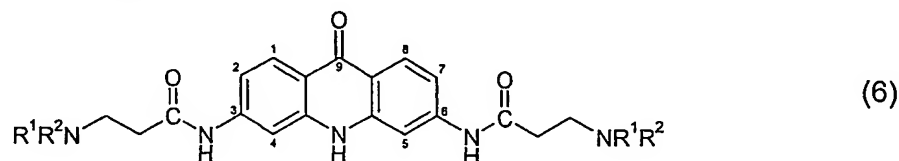


In one preferred embodiment, the compounds are acridones and have the following formula, wherein -NR¹R² is a terminal amino group:



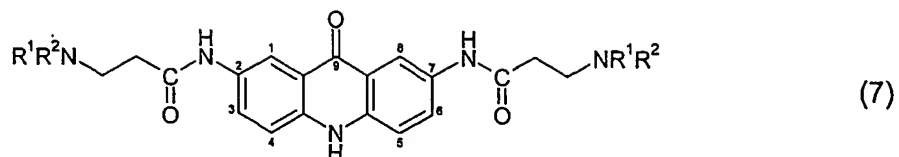
15

In one preferred embodiment, the compounds are 3,6-disubstituted acridones, and have the following formula, wherein -NR¹R² is a terminal amino group:

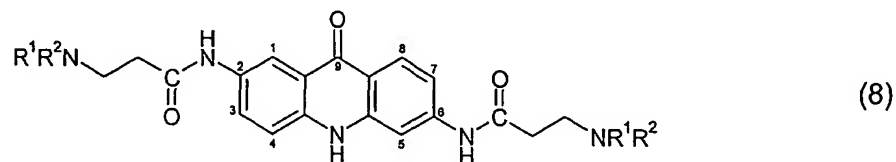


- In one preferred embodiment, the compounds are 2,7-disubstituted acridones, and
 20 have the following formula, wherein -NR¹R² is a terminal amino group:

- 9 -

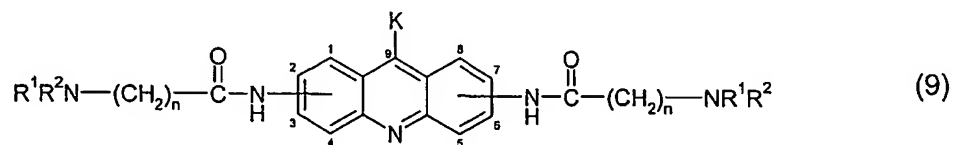


In one preferred embodiment, the compounds are 2,6-disubstituted acridones (alternatively referred to as 3,7-disubstituted acridones), and have the following formula, wherein $-NR^1R^2$ is a terminal amino group:

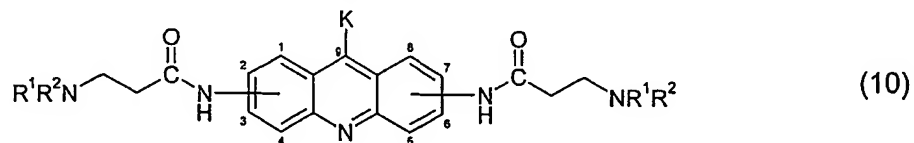


5

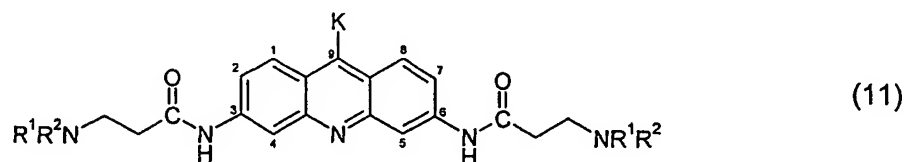
In another embodiment, the compounds are acridines, and have the following formula, wherein n is as defined above, $-NR^1R^2$ is a terminal amino group, and K is a 9-substituent:



10 In one preferred embodiment, the compounds are acridines, and have the following formula, wherein $-NR^1R^2$ is a terminal amino group and K is a 9-substituent:

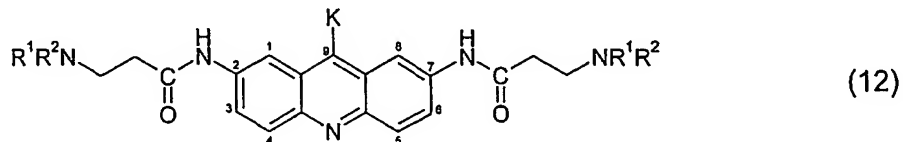


15 In one preferred embodiment, the compounds are 3,6,9-trisubstituted acridines, and have the following formula, wherein $-NR^1R^2$ is a terminal amino group and K is a 9-substituent:



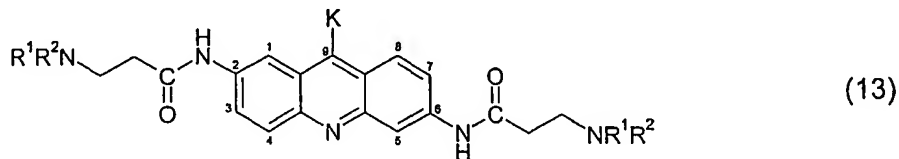
- 10 -

In one preferred embodiment, the compounds are 2,7,9-trisubstituted acridines, and have the following formula, wherein $-NR^1R^2$ is a terminal amino group and K is a 9-substituent:



5

In one preferred embodiment, the compounds are 2,6,9-trisubstituted acridines (also referred to as 3,7,9-trisubstituted acridines), and have the following formula, wherein $-NR^1R^2$ is a terminal amino group and K is a 9-substituent:



10 Terminal Amino Groups, $-NR^1R^2$

The term "terminal amino group," as used herein, pertains to a amino group of the formula $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, C_{1-7} alkyl, C_{3-20} heterocyclyl, or C_{5-20} aryl, which may themselves
15 be substituted.

In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is a secondary amino group, and one of R^1 and R^2 is -H.

20 In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is a tertiary amino group, and neither R^1 nor R^2 is -H.

In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is a tertiary amino group, neither R^1 nor R^2 is -H, and R^1 and R^2 are the same.

25

- 11 -

In one preferred embodiment, R^1 and R^2 are each independently C_{1-7} alkyl, which is optionally substituted.

In one preferred embodiment, R^1 and R^2 are each independently aliphatic saturated
5 C_{1-7} alkyl, which is optionally substituted.

In one preferred embodiment, R^1 and R^2 are each independently aliphatic saturated unsubstituted C_{1-7} alkyl.

10 In one preferred embodiment, R^1 and R^2 are each independently -Me, -Et, -nPr, -iPr, -nBu, or -tBu.

In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is $-N(Me)_2$,
-N(Et)₂, -N(nPr)₂, -N(iPr)₂, -N(nBu)₂, or -N(tBu)₂.

15

In one preferred embodiment, R^2 is H and R^1 is C_{1-7} alkyl, which is optionally substituted.

In one preferred embodiment, R^2 is H and R^1 is aliphatic saturated C_{1-7} alkyl,
20 which is optionally substituted.

In one preferred embodiment, R^2 is H and R^1 is aliphatic saturated unsubstituted C_{1-7} alkyl.

25 In one preferred embodiment, R^2 is H and R^1 is -Me, -Et, -nPr, -iPr, -nBu, or -tBu.

In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is -NHMe, -NH₂,
-NH(nPr), -NH(iPr), -NH(nBu), or -NH(tBu).

30

In one preferred embodiment, R^1 and R^2 are each independently C_{5-20} aryl, which is optionally substituted.

In one preferred embodiment, R¹ and R² are each independently C₅₋₂₀carboaryl, which is optionally substituted.

In one preferred embodiment, R¹ and R² are each independently C₅₋₂₀heteroaryl,
5 which is optionally substituted.

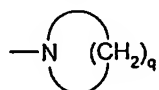
In one preferred embodiment, R¹ and R² are each independently phenyl, which is optionally substituted.

10 Alternatively, R¹ and R², taken together with the nitrogen atom to which they are attached, may form a heterocyclic ring having from 3 to 8 ring atoms (e.g., a C₃₋₈heterocyclyl group), more preferably 5 to 8 ring atoms (e.g., a C₅₋₈heterocyclyl group), which heterocyclic ring may be saturated, partially unsaturated, or fully unsaturated, and is optionally substituted.

15 In one preferred embodiment, R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring having from 3 to 8 ring atoms (e.g., a C₃₋₈heterocyclyl group), more preferably 5 to 8 ring atoms (e.g., a C₅₋₈heterocyclyl group), which heterocyclic ring is optionally substituted.

20 In one preferred embodiment, R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring having from 3 to 8 ring atoms (e.g., a C₃₋₈heterocyclyl group), more preferably 5 to 8 ring atoms (e.g., a C₅₋₈heterocyclyl group), wherein only one of said ring atoms is nitrogen, and all
25 others are carbon, and which heterocyclic ring is optionally substituted.

In one preferred embodiment, R¹ and R², taken together with the nitrogen atom to which they are attached form a cyclic amino group of the following formula, wherein q is an integer from 2 to 7, and wherein said group is optionally substituted:



- 13 -

In one preferred embodiment, q is an integer from 3 to 7.

In one preferred embodiment, q is an integer from 4 to 7.

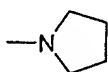
In one preferred embodiment, q is an integer from 4 to 6.

In one preferred embodiment, q is 4 or 5.

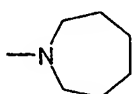
5

In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is one of the following cyclic amino groups, and is optionally substituted:

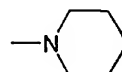
azolidino
(pyrrolidino)



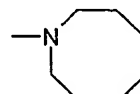
perhydroazepino



perhydroazino
(piperidino)



perhydroazocino



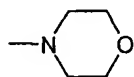
- 10 In one preferred embodiment, R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 3 to 8 ring atoms (e.g., a C_{3-8} heterocyclyl group), more preferably 5 to 8 ring atoms (e.g., a C_{3-8} heterocyclyl group), wherein said ring has at least two heteroatoms selected from nitrogen, oxygen, and sulfur, which heterocyclic ring may saturated, partially
15 unsaturated, or fully unsaturated, and is optionally substituted.

- In one preferred embodiment, R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring having from 3 to 8 ring atoms (e.g., a C_{3-8} heterocyclyl group), more preferably 5 to 8 ring atoms (e.g., a
20 C_{3-8} heterocyclyl group), wherein said ring has at least two heteroatoms selected from nitrogen, oxygen, and sulfur, which heterocyclic ring is optionally substituted.

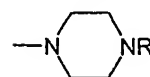
In one preferred embodiment, the terminal amino group, $-NR^1R^2$, is one of the following groups, and is optionally substituted:

- 14 -

morpholino



piperazino

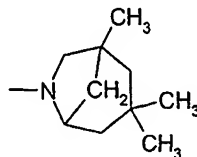


wherein R is an amino substituent, for example, hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl.

In one preferred embodiment, -NR¹R², is piperazino, and R is -Me or -Et.

5

When R¹ and R², taken together with the nitrogen atom, form a heterocyclic ring, the ring may optionally be bridged, fused, and/or spiro in nature, and is optionally substituted. An example of such a terminal amino group, -NR¹R², is shown below:



10

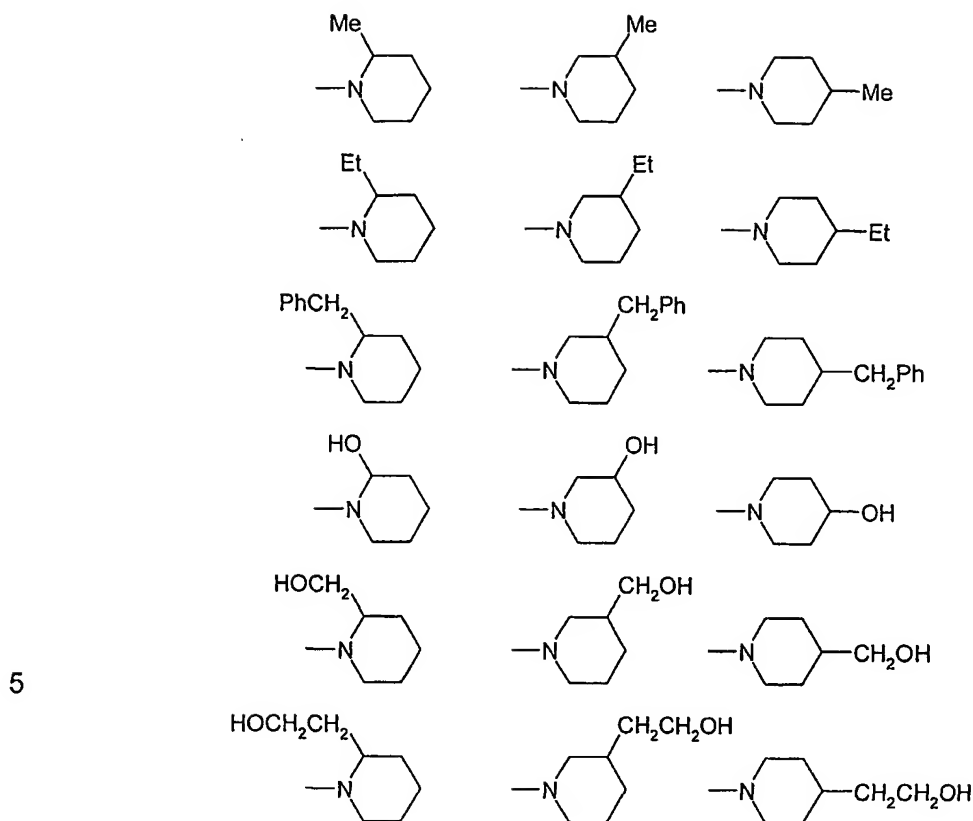
As mentioned above, the groups R¹ and R², or the heterocyclic ring formed from R¹ and R² and the nitrogen atom to which they are attached, are optionally substituted.

15 For example, in one preferred embodiment, R¹ and R² and the nitrogen atom to which they are attached form a cyclic amino group, -NR¹R², which has one or more substituents selected from: C₁₋₇alkyl, C₃₋₂₀aryl-C₁₋₇alkyl, C₃₋₂₀aryl, C₁₋₇alkyl-C₃₋₂₀aryl, hydroxy C₁₋₇hydroxyalkyl, and C₁₋₇aminoalkyl.

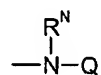
20 In one preferred embodiment, R¹ and R² and the nitrogen atom to which they are attached form a cyclic amino group, -NR¹R², which has one or more substituents selected from: -Me, -Et, -CH₂Ph, -OH, -CH₂OH, -CH₂CH₂OH, -CH₂NH₂, and -CH₂CH₂NH₂.

25 In one preferred embodiment, the terminal amino group, -NR¹R², is one of the following substituted cyclic amino groups:

- 15 -

9-Substituents, K

- 10 In the above acridine compounds, wherein K is a 9-substituent, K is a group of the formula:

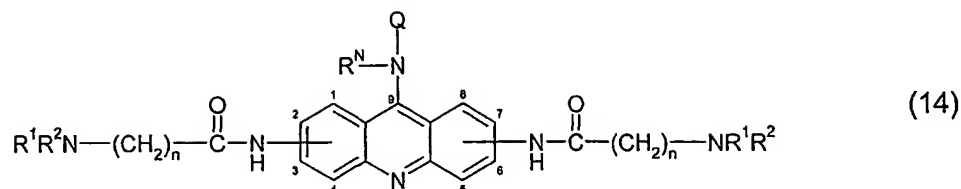


wherein:

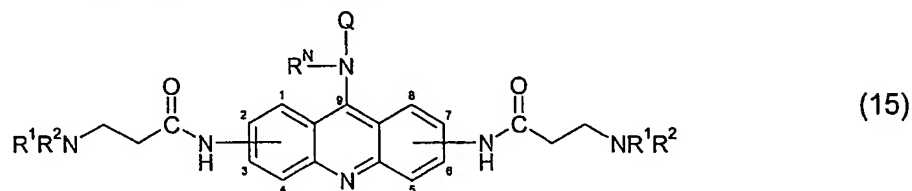
- 15 R^{N} is an amino substituent and is hydrogen, C_{1-7} alkyl, C_{3-20} heterocyclyl, or C_{5-20} aryl; and,
 Q is C_{1-7} alkyl, C_{3-20} heterocyclyl, or C_{5-20} aryl, and is optionally substituted.

Thus, the acridine compounds have the following formula:

- 16 -



And, as mentioned above, in one preferred embodiment wherein n is 2, the acridine compounds have the following formula:



5 The Nitrogen Substituent, R^N

In one preferred embodiment, R^N is hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl.

10 In one preferred embodiment, R^N is hydrogen or C₁₋₇alkyl.

In one preferred embodiment, R^N is hydrogen or aliphatic saturated C₁₋₇alkyl.

In one preferred embodiment, R^N is -H, -Me, -Et, -nPr, or -iPr.

15

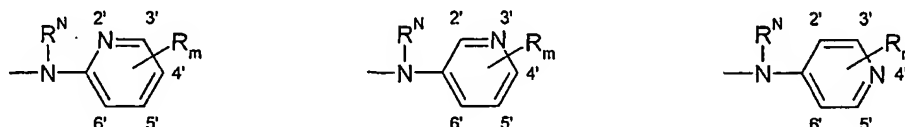
In one preferred embodiment, R^N is -H.

The Moiety, Q, as Optionally Substituted Aryl Group

20 In one embodiment, Q is a C₅₋₂₀aryl group, which is optionally substituted. In one embodiment, Q is a C₆aryl group (e.g., C₆carboaryl or C₆heteroaryl), which is optionally substituted.

- 17 -

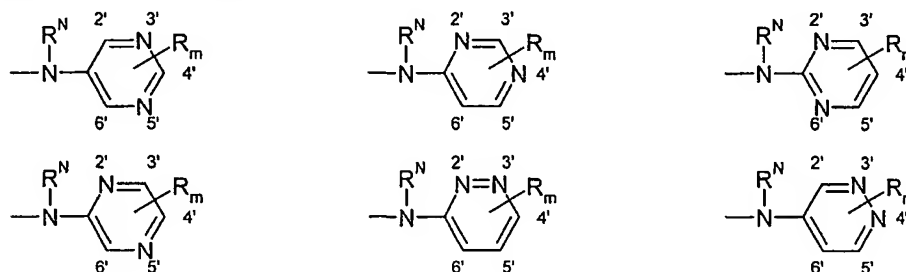
In one embodiment, Q is an azinyl (pyridyl) group which is optionally substituted, and K is a group of the formula:



wherein m is an integer from 0 to 4, and each R is independently a substituent as defined herein.

5

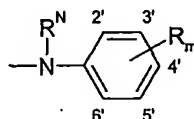
In one embodiment, Q is a substituted diazinyl (e.g., pyridazinyl, pyrimidinyl, pyrazinyl) group which is optionally substituted, and K is, for example, a group having one of the following formulae:



wherein m is an integer from 0 to 3, and each R is independently a substituent as defined herein.

10

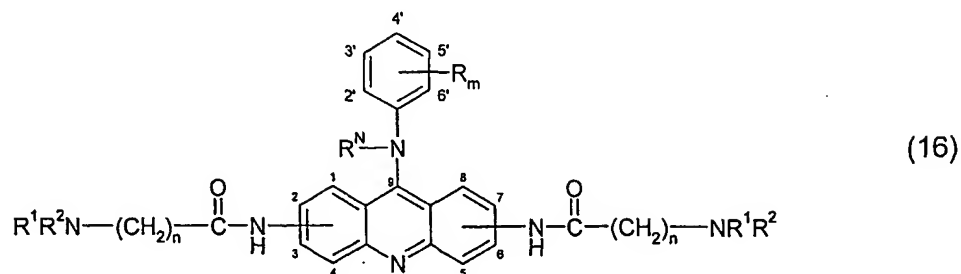
In one embodiment, Q is a phenyl group which is optionally substituted, and K is a group of the formula:



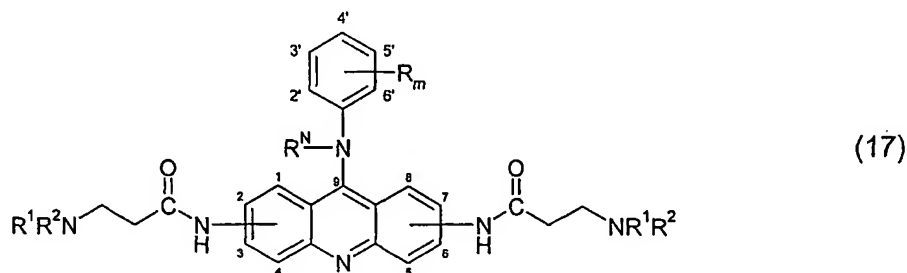
15 wherein m is an integer from 0 to 5, and each R is independently a substituent as defined herein.

- 18 -

In this embodiment, the acridine compounds have the formula:



In one preferred embodiment wherein n is 2, the acridine compounds have the following formula:



5

In one preferred embodiment, m is an integer from 0 to 4.

In one preferred embodiment, m is an integer from 0 to 3.

In one preferred embodiment, m is an integer from 0 to 2.

In one preferred embodiment, m is 0 or 1.

10 In one preferred embodiment, m is an integer from 1 to 5.

In one preferred embodiment, m is an integer from 1 to 4.

In one preferred embodiment, m is an integer from 1 to 3.

In one preferred embodiment, m is 1 or 2.

In one preferred embodiment, m is 5.

15 In one preferred embodiment, m is 4.

In one preferred embodiment, m is 3.

In one preferred embodiment, m is 2.

In one preferred embodiment, m is 1.

In one preferred embodiment, m is 0.

20

- 19 -

If the phenyl group has less than the full complement of ring substituents, R, they may be arranged in any combination. For example, if m is 1, R may be in the 2'-, 3'-, 4'-, 5'-, or 6'-position. Similarly, if m is 2, the two R groups may be in, for example, the 2',3'-, 2',4'-, 2',5'-, 2',6'-, 3',4'-, or 3',5'-positions. If m is 3, the three R
5 groups may be in, for example, the 2',3',4'-, 2',3',5'-, 2',3',6'-, or 3',4',5'-positions.

Examples of some preferred phenyl substituents include, but are not limited to, halo, amino, hydroxy, ether (e.g., C₁₋₇alkoxy), thio, thioether (e.g., C₁₋₇alkylthio), C₁₋₇alkyl, C₁₋₇haloalkyl, acyl (e.g., C₁₋₇alkylacyl), amido (e.g., C₁₋₇alkylamido),
10 carboxy, cyano, and aminoalkyl.

Examples of substituted phenyl groups which are suitable as Q include, but are not limited to, the following:

15 monohalophenyl, for example,
4'-fluorophenyl, 3'-fluorophenyl, 2'-fluorophenyl;
4'-chlorophenyl, 3'-chlorophenyl, 2'-chlorophenyl;
4'-bromophenyl, 3'-bromophenyl, 2'-bromophenyl.

20 dihalophenyl, for example,
2',3'-difluorophenyl, 2',3'-dichlorophenyl;
2',4'-difluorophenyl, 2',4'-dichlorophenyl;
2',5'-difluorophenyl, 2',5'-dichlorophenyl;
3',4'-difluorophenyl, 3',4'-dichlorophenyl;
25 3',5'-difluorophenyl, 3',5'-dichlorophenyl.

monoaminophenyl, for example,
4'-aminophenyl, 3'-aminophenyl, 2'-aminophenyl.

30 diaminophenyl, for example,
2',3'-diaminophenyl, 2',4'-diaminophenyl, 2',5'-diaminophenyl,
3',4'-diaminophenyl, 3',5'-diaminophenyl.

- 20 -

monohydroxyphenyl, for example,
4'-hydroxyphenyl, 3'-hydroxyphenyl, 2'-hydroxyphenyl.

monomethoxyphenyl, for example,
5 4'-methoxyphenyl, 3'-methoxyphenyl, 2'-methoxyphenyl.

monothiophenyl, for example,
4'-thiophenyl, 3'-thiophenyl, 2'-thiophenyl.

10 monomethylthiophenyl, for example,
4'-methylthiophenyl, 3'-methylthiophenyl, 2'-methylthiophenyl.

monomethylphenyl, for example,
4'-methylphenyl, 3'-methylphenyl, 2'-methylphenyl.

15 monotrifluoromethylphenyl, for example,
4'-trifluoromethylphenyl, 3'-trifluoromethylphenyl, 2'-trifluoromethylphenyl.

monoacetylphenyl, for example,
20 4'-acetylphenyl, 3'-acetylphenyl, 2'-acetylphenyl.

monoamidophenyl, for example,
4'-amidophenyl, 3'-amidophenyl, 2'-amidophenyl.
4'-(methyلامido)phenyl, 3'-(methyلامido)phenyl, 2'-(methyلامido)phenyl.

25 monocarboxyphenyl, for example,
4'-carboxyphenyl, 3'-carboxyphenyl, 2'-carboxyphenyl.

monocyanophenyl, for example,
30 4'-cyanophenyl, 3'-cyanophenyl, 2'-cyanophenyl.

- 21 -

mono(aminoalkyl)phenyl, for example,

4'-aminoalkylphenyl, 3'-aminoalkylphenyl, 2'-aminoalkylphenyl;

4'-aminomethylphenyl, 3'-aminomethylphenyl, 2'-aminomethylphenyl;

4'-aminoethylphenyl, 3'-aminoethylphenyl, 2'-aminoethylphenyl.

5

monohalo-mono(aminoalkyl)phenyl, for example,

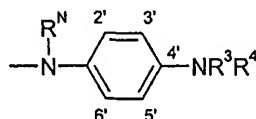
2'-halo-4'-aminoalkylphenyl, 2'-halo-3'-aminoalkylphenyl, 3'-halo-

2'-aminoalkylphenyl, 3'-halo-4'-aminoalkylphenyl,

4'-halo-2'-aminoalkylphenyl, 4'-halo-3'-aminoalkylphenyl.

10

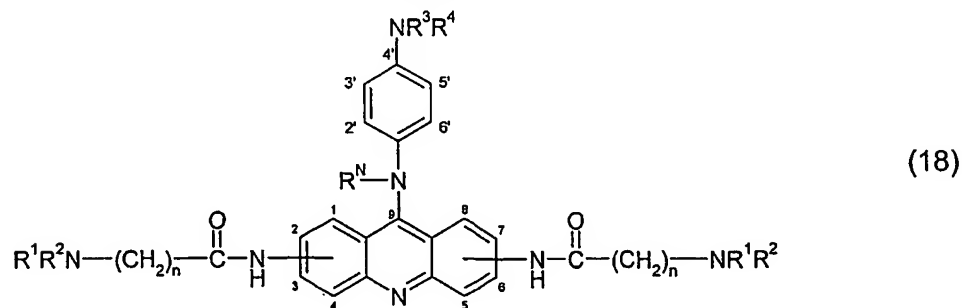
In one preferred embodiment, Q is a 4'-aminophenyl group, and K is a group of the formula:



wherein $-NR^3R^4$ is as defined above for $-NR^1R^2$.

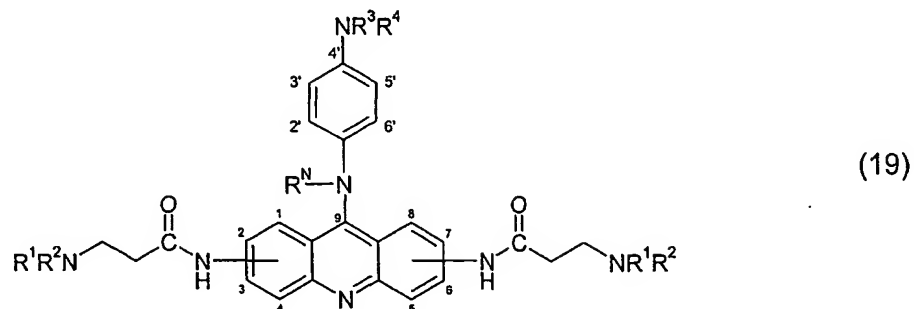
15

In this embodiment, the acridine compounds have the formula:

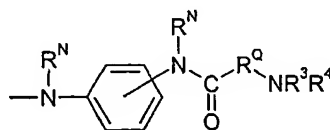


- 22 -

In one preferred embodiment wherein n is 2, the acridine compounds have the following formula:

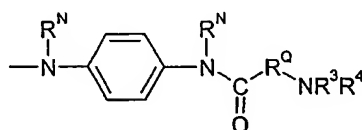


In one preferred embodiment, Q is an (amino-alkyl-amido) phenyl group, and K is a group of the formula:



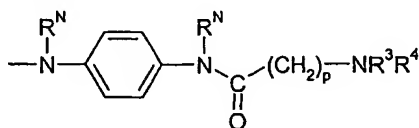
wherein R^Q is a C_{1-10} alkylene group, and $-NR^3R^4$ is as defined above for $-NR^1R^2$.

In one preferred embodiment, Q is a 4'-(amino-alkyl-amido) phenyl group, and K is a group of the formula:



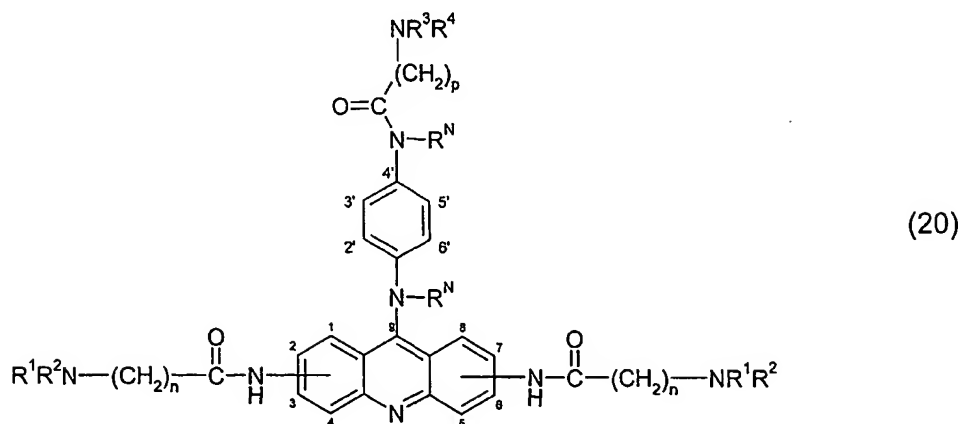
wherein R^Q is a C_{1-10} alkylene group, and $-NR^3R^4$ is as defined above for $-NR^1R^2$.

In one preferred embodiment, Q is $-(CH_2)_p-$, wherein p is an integer from 1 to 10, and K has the following formula:

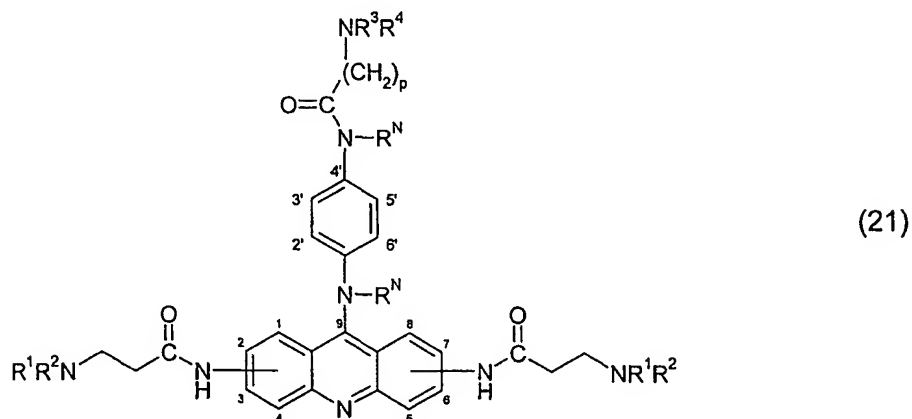


- 23 -

In this embodiment, the acridine compounds have the formula:



In one preferred embodiment wherein n is 2, the acridine compounds have the following formula:

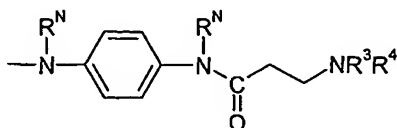


5

In one embodiment, p is an integer from 1 to 8. In one embodiment, p is an integer from 1 to 6. In one embodiment, p is an integer from 1 to 4. In one embodiment, p is an integer from 2 to 6. In one embodiment, p is an integer from 2 to 4. In one embodiment, p is 2 or 3.

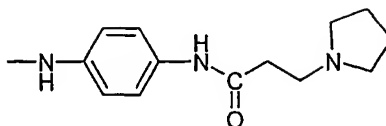
10

In one embodiment, p is 2, and K is a group of the formula:

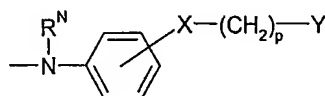


- 24 -

In one embodiment, K is a group of the formula:



5 In one preferred embodiment, Q is a certain substituted phenyl group, and K is a group of the formula:



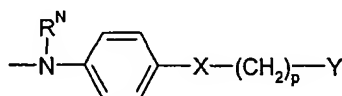
wherein:

X is $-N(N^R)-$, $-CH_2-$, $-O-$, or $-S-$;

Y is $-OH$, $-OR^Y$, or $-NR^3R^4$;

- 10 R^Y is C_{1-7} alkyl, C_{3-20} heterocyclyl, or C_{5-20} aryl;
 $-NR^3R^4$ is as defined above for $-NR^1R^2$; and,
 p is an integer from 1 to 10, as defined above.

15 In one preferred embodiment, the substituent is para, and K is a group of the formula:



In one embodiment, X is $-N(N^R)-$, $-CH_2-$, $-O-$, or $-S-$, and Y is $-NR^3R^4$.

20 In one embodiment, X is $-O-$, or $-S-$, and Y is $-OH$, $-OR^Y$, or $-NR^3R^4$.

In one embodiment, X is $-O-$, or $-S-$, and Y is $-NR^3R^4$.

In one embodiment, X is $-O-$, and Y is $-NR^3R^4$.

25

In one embodiment, X is $-N(N^R)-$ and Y is $-OH$, $-OR^Y$, or $-NR^3R^4$.

In one embodiment, X is $-N(N^R)-$ and Y is $-NR^3R^4$.

The Moiety, Q, as Optionally Substituted Alkyl Group

In one embodiment, Q is a C₁₋₇alkyl group, which is optionally substituted.

5

In one embodiment, Q is a substituted C₁₋₇alkyl group, for example, a C₁₋₇alkyl group substituted with one or more amino groups, one or more hydroxy groups, one or more ether groups, one or more carboxy groups, one or more C₃₋₂₀heterocyclyl groups, one or more C₅₋₂₀aryl, etc.

10

In one embodiment, Q is an amino substituted C₁₋₇alkyl group, that is, a C₁₋₇alkyl group substituted with one or more amino groups.

In one embodiment, Q is a hydroxy substituted C₁₋₇alkyl group, that is, a C₁₋₇alkyl group substituted with one or more hydroxy groups.

15

In one embodiment, Q is a ether substituted C₁₋₇alkyl group, that is, a C₁₋₇alkyl group substituted with one or more ether groups. For example, Q may be -CH₂CH₂-OMe.

20

In one embodiment, Q is a carboxy substituted C₁₋₇alkyl group, that is, a C₁₋₇alkyl group substituted with one or more carboxy groups.

In one embodiment, Q is a C₃₋₂₀heterocyclyl substituted C₁₋₇alkyl group, that is, a C₁₋₇alkyl group substituted with one or more C₃₋₂₀heterocyclyl groups. For example, Q may be -CH₂CH₂-(N-methyl-pyrrolidin-2-yl).

25

In one embodiment, Q is a C₅₋₂₀aryl substituted C₁₋₇alkyl group, that is, a C₁₋₇alkyl group substituted with one or more C₅₋₂₀aryl groups. For example, Q may be -CH₂CH₂-(pyrid-3-yl).

30

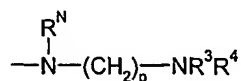
- 26 -

In one embodiment, Q is an amino substituted aliphatic saturated C₁₋₇alkyl group, that is, an aliphatic saturated C₁₋₇alkyl group substituted with one or more amino groups.

- 5 In one embodiment, Q is an amino substituted linear saturated C₁₋₇alkyl group, that is, a linear saturated C₁₋₇alkyl group substituted with one or more amino groups.

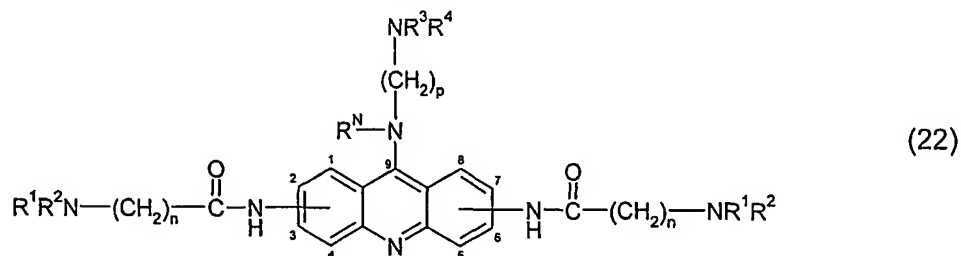
In one embodiment, Q is a terminally amino substituted linear saturated C₁₋₇alkyl group, that is, a linear saturated C₁₋₇alkyl group substituted with a terminal amino group, and K is a group of the formula:

- 10

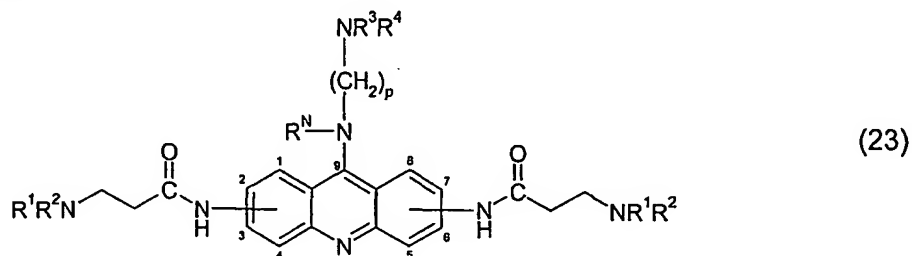


wherein p is an integer from 1 to 10, and the group -NR³R⁴ is as defined above for -NR¹R².

- 15 In this embodiment, the acridine compounds have the formula:

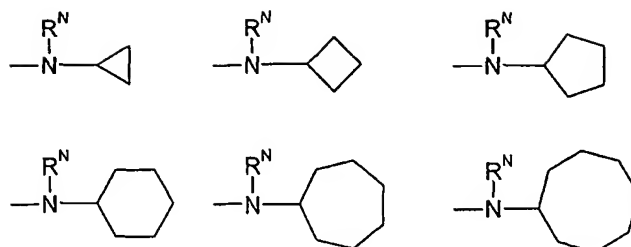


In one preferred embodiment wherein n is 2, the acridine compounds have the following formula:

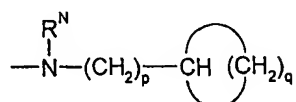


- 20 In one embodiment, p is an integer from 1 to 8. In one embodiment, p is an integer from 1 to 6. In one embodiment, p is an integer from 1 to 4. In one embodiment, p

- 28 -



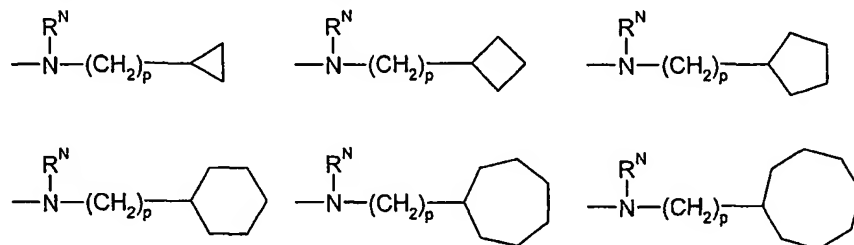
In one embodiment, Q is, or comprises, an alicyclic saturated C₁₋₇alkyl group, and K is a group of the formula:



5

wherein p and q are as defined above, and wherein the cyclic group is optionally substituted. Examples of preferred substituents include halo, hydroxy, amino, and C₁₋₇alkyl.

10 In one embodiment, Q is, or comprises, an alicyclic saturated C₁₋₇alkyl group, and K is a group of one of the following formulae:



wherein p is as defined above, and wherein the cyclic group is optionally substituted.

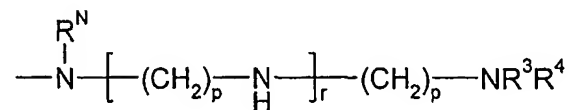
15

Examples of other embodiments, wherein Q is, or comprises, an alicyclic saturated C₁₋₇alkyl group, which is optionally substituted include the following:



- 29 -

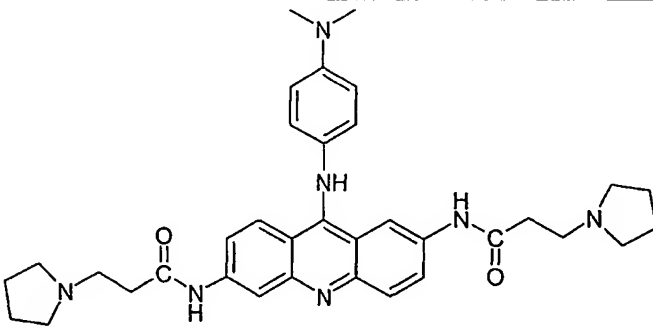
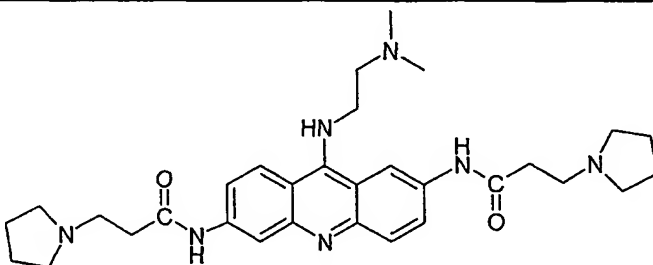
In one embodiment, Q is an amino substituted polyaminoalkylene group, and K is a group of the formula:



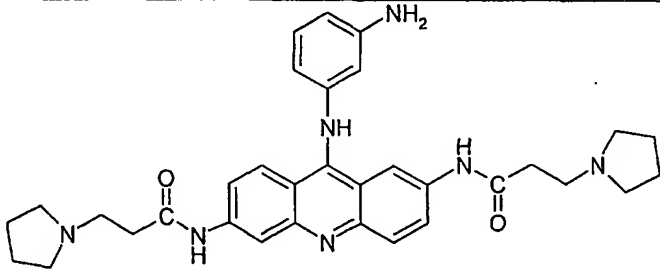
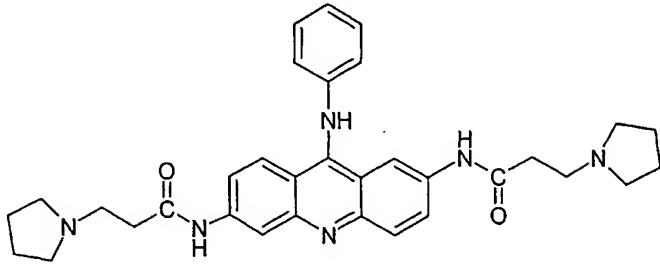
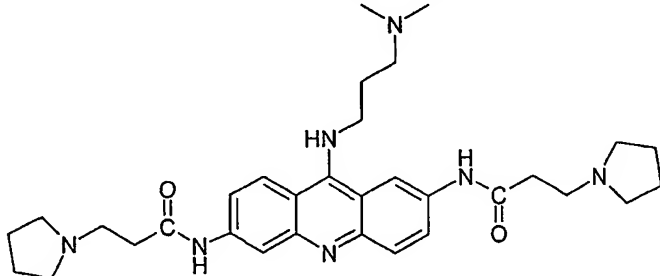
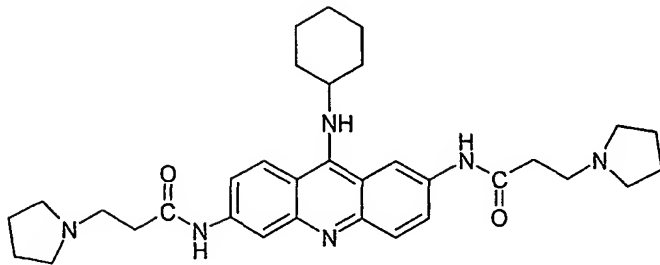
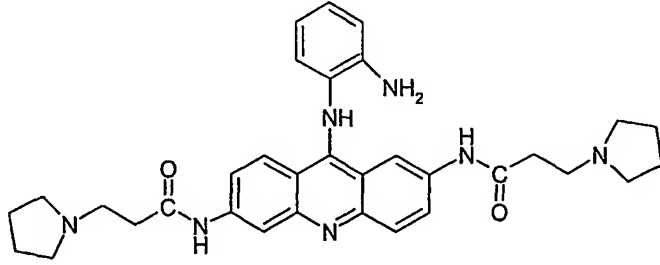
- wherein p is as defined above, r is an integer from 1 to 4, and the group -NR³R⁴ is as defined above for -NR¹R². In one embodiment, r is an integer from 1 to 3. In one embodiment, r is 1 or 2. In one embodiment, r is 1.

Examples of Specific Embodiments

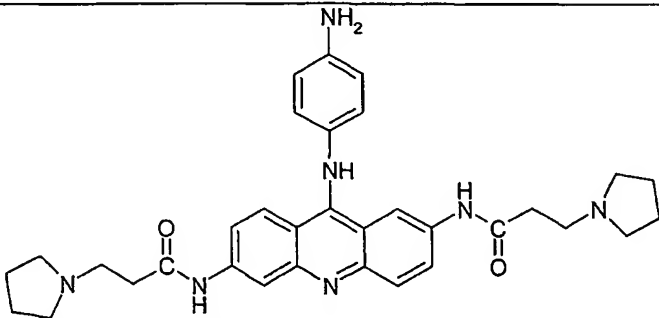
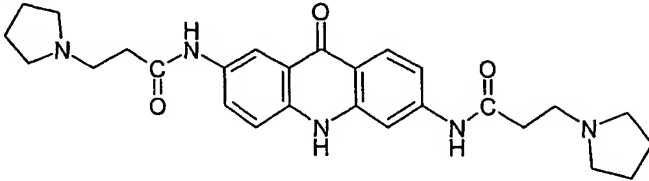
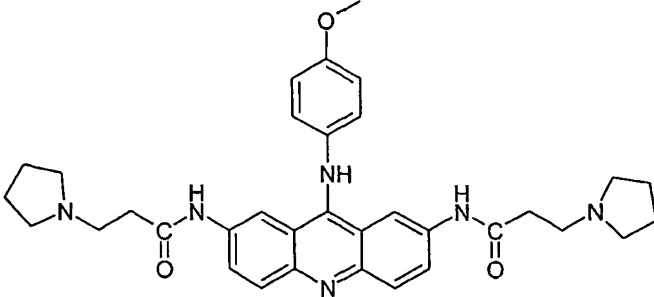
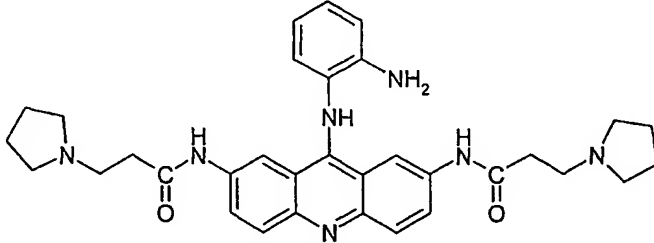
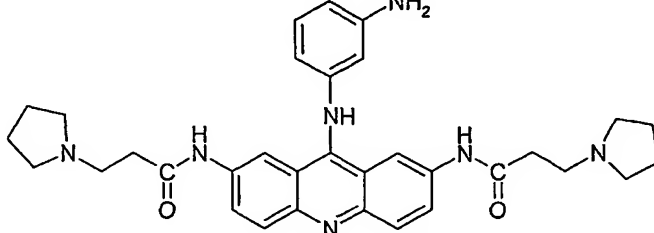
- 10 Some individual embodiments of the present invention include the following compounds:

Class	# Free Base HCl Salt	Structure
2,6,9- ine	1 BSU-SB- 36/188 SB-ACI-18	
2,6,9- ine	2 BSU-SB- 36/190 SB-ACI-19	

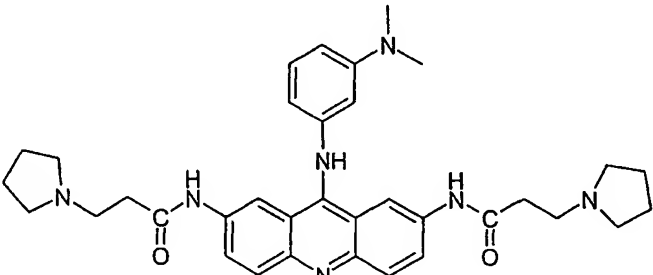
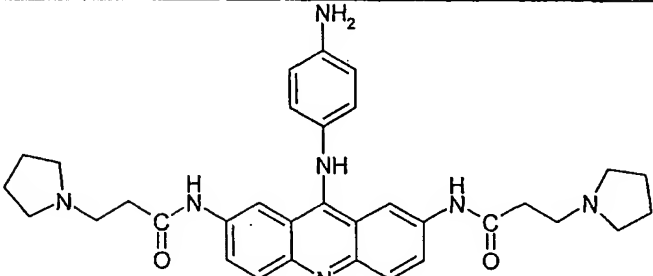
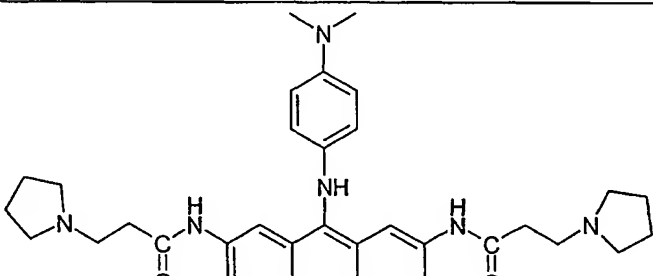
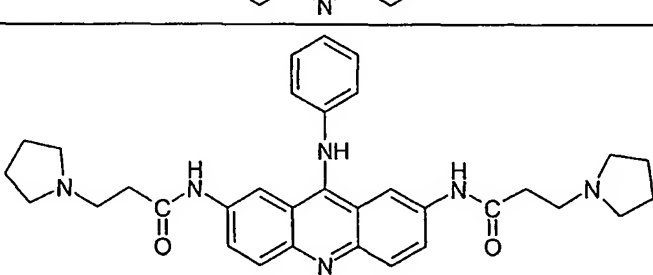
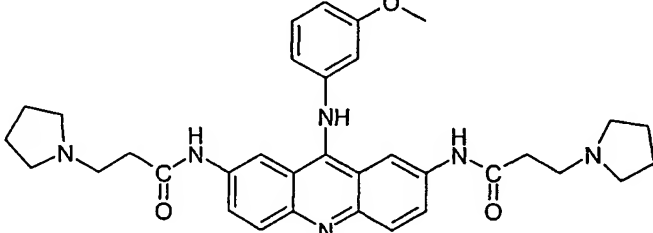
- 30 -

Class	# Free Base HCl Salt	Structure
2,6,9- ine	3 BSU-SB- 36/194 SB-ACI-17	 <chem>Nc1ccc(NC2=CC=C3C=C(NC(=O)CCN4CCCC4)C=CC(=C3C=C2)NC(=O)CCN5CCCC5)cc1</chem>
2,6,9- ine	4 BSU-SB- 36/196 SB-ACI-22	 <chem>c1ccc(NC2=CC=C3C=C(NC(=O)CCN4CCCC4)C=CC(=C3C=C2)NC(=O)CCN5CCCC5)cc1</chem>
2,6,9- ine	5 BSU-SB- 36/198 SB-ACI-20	 <chem>CN(C)CCNC2=CC=C3C=C(NC(=O)CCN4CCCC4)C=CC(=C3C=C2)NC(=O)CCN5CCCC5</chem>
2,6,9- ine	6 BSU-SB- 36/200 SB-ACI-21	 <chem>C1CCCCC1NC2=CC=C3C=C(NC(=O)CCN4CCCC4)C=CC(=C3C=C2)NC(=O)CCN5CCCC5</chem>
2,6,9- ine	7 BSU-SB- 36/202 SB-ACI-16	 <chem>Nc1cccc(NC2=CC=C3C=C(NC(=O)CCN4CCCC4)C=CC(=C3C=C2)NC(=O)CCN5CCCC5)c1</chem>

- 31 -

Class	# Free Base HCl Salt	Structure
2,6,9- ine	8 JH-ACI-104 JH-ACI-105	
2,6- one	9 AR-ACO-10 AR-ACO-11	
2,7,9- ine	10 JM-ACI-10 JM-ACI-11	
2,7,9- ine	11 JM-ACI-29 JM-ACI-30	
2,7,9- ine	12 JM-ACI-31 JM-ACI-32	

- 32 -

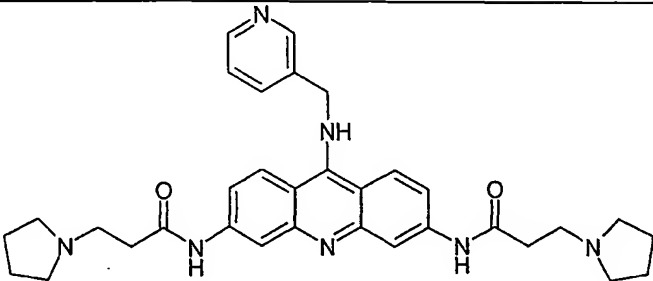
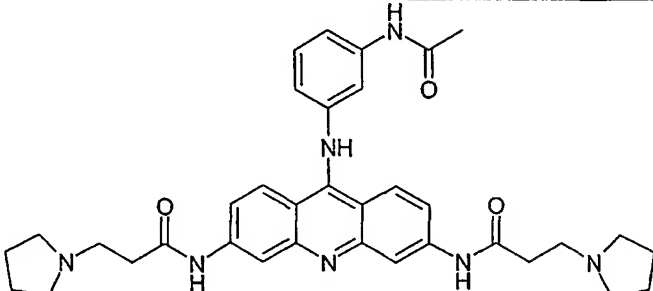
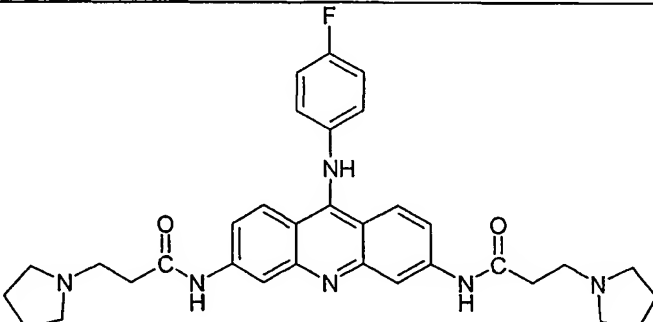
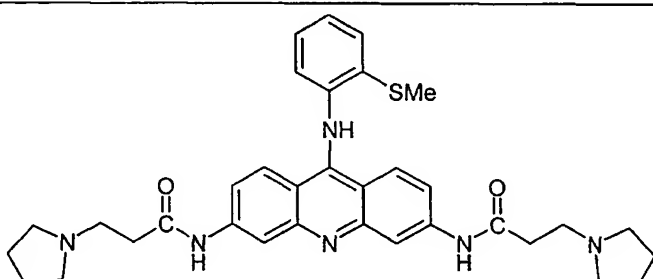
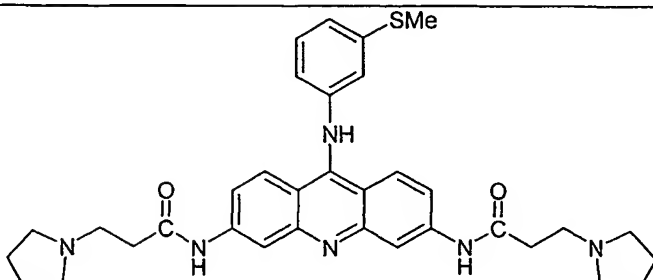
Class	# Free Base HCl Salt	Structure
2,7,9- ine	13 JM-ACI-33 JM-ACI-34	 <chem>CN(C)c1ccc(Nc2ccc(NC(=O)CCN3CCCC3)cc2c3ccc(NC(=O)CCN4CCCC4)cc3n4)cc1</chem>
2,7,9- ine	14 JM-ACI-35 JM-ACI-36	 <chem>Nc1ccc(Nc2ccc(NC(=O)CCN3CCCC3)cc2c3ccc(NC(=O)CCN4CCCC4)cc3n4)cc1</chem>
2,7,9- ine	15 JM-ACI-37 JM-ACI-38	 <chem>CN(C)c1ccc(Nc2ccc(NC(=O)CCN3CCCC3)cc2c3ccc(NC(=O)CCN4CCCC4)cc3n4)cc1</chem>
2,7,9- ine	16 JM-ACI-39 JM-ACI-40	 <chem>c1ccc(Nc2ccc(NC(=O)CCN3CCCC3)cc2c3ccc(NC(=O)CCN4CCCC4)cc3n4)cc1</chem>
2,7,9- ine	17 JM-ACI-41 JM-ACI-42	 <chem>COc1ccc(Nc2ccc(NC(=O)CCN3CCCC3)cc2c3ccc(NC(=O)CCN4CCCC4)cc3n4)cc1</chem>

- 33 -

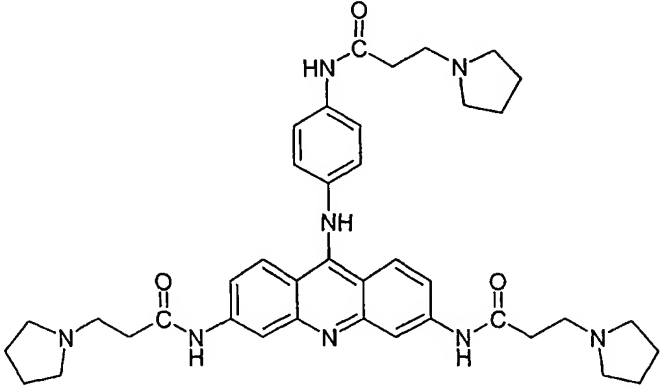
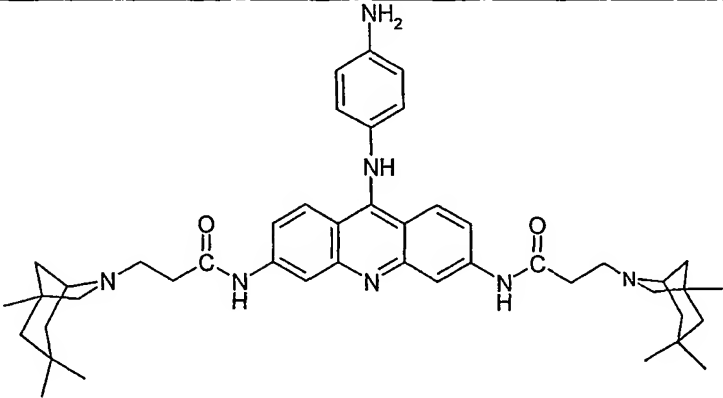
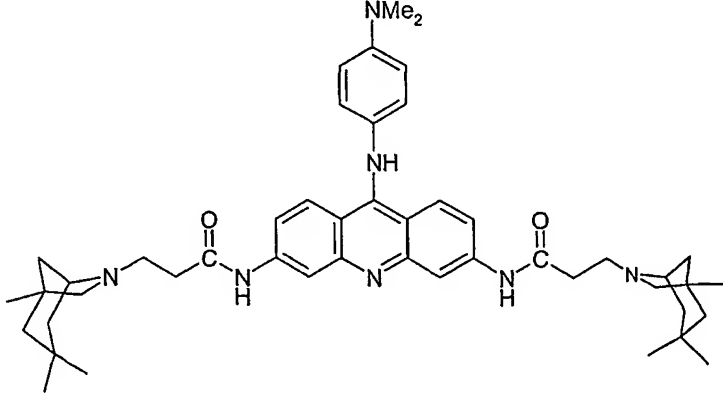
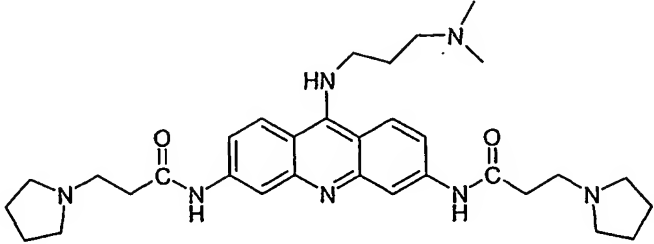
Class	# Free Base HCl Salt	Structure
2,7,9- ine	18 JM-ACI-45 JM-ACI-46	
2,7- one	19 BR-ACO-16 BR-ACO-9	
2,7- one	20 BR-ACO-17 BR-ACO-10	
2,7- one	21 JH-ACO-23 JH-ACO-22	
2,7- one	22 JH-ACO-27 JH-ACO-28	
2,7- one	23 JM-ACO-06 JM-ACO-07	
2,7- one	24 JM-ACO-08 JM-ACO-09	
2,7- one	25 JM-ACO-11 JM-ACO-12	

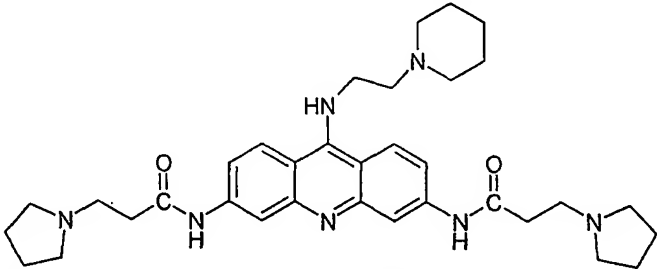
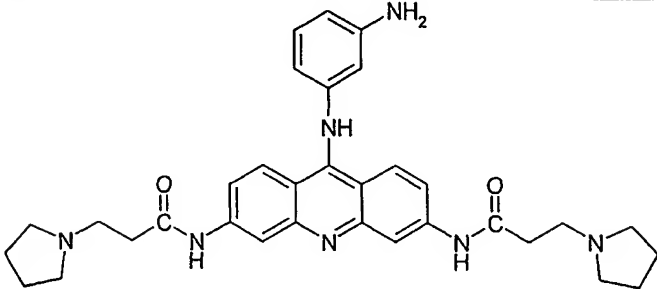
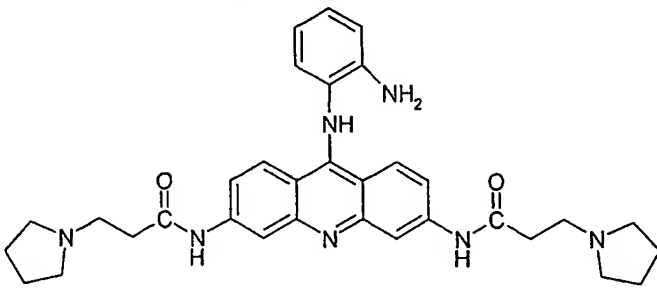
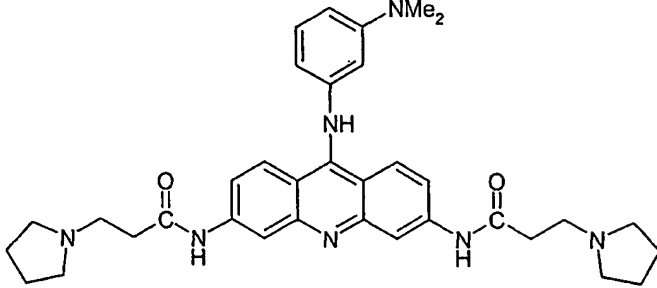
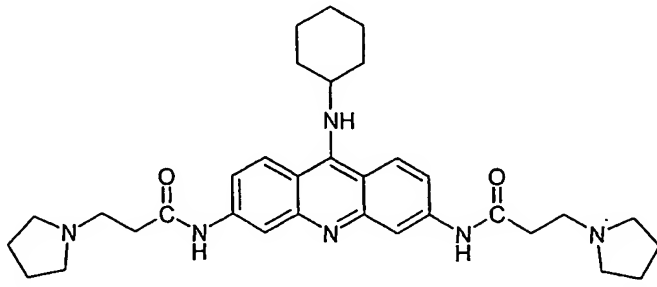
- 34 -

Class	# Free Base HCl Salt	Structure
3,6,9- ine	26 BR-ACO-21 BR-ACO-19	 <chem>CN(C)c1ccc(Nc2nc3c(cc2)ccc(NC(=O)CCN3)c3)cc1</chem>
3,6,9- ine	27 BR-ACO-22 BR-ACO-20	 <chem>Nc1ccc(Nc2nc3c(cc2)ccc(NC(=O)CCN3)c3)cc1</chem>
3,6,9- ine	28 BSU-SB- 36/152 SB-ACI-11	 <chem>CN(C)CCNc1nc2c(cc1)ccc(NC(=O)CCN2)c2</chem>
3,6,9- ine	29 BSU-SB- 36/158 SB-ACI-12	 <chem>CN1CCCC1CCNc1nc2c(cc1)ccc(NC(=O)CCN2)c2</chem>

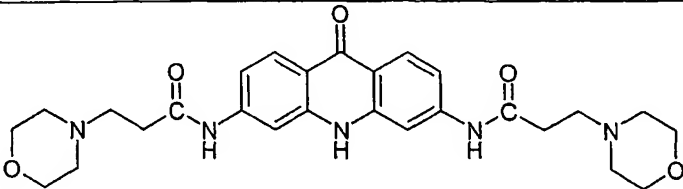
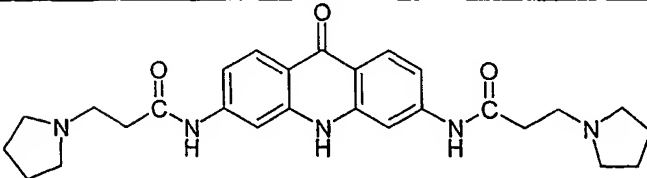
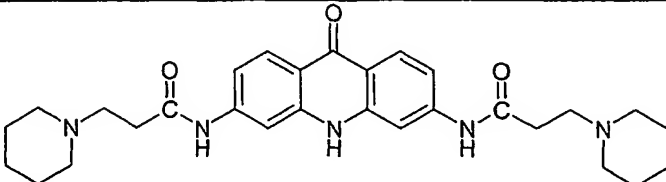
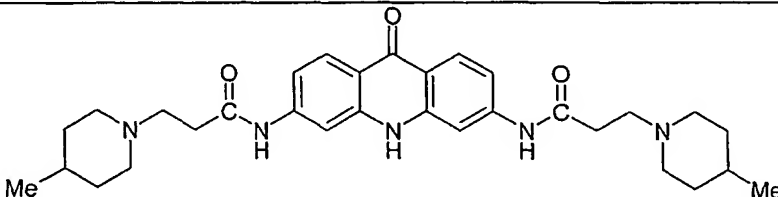
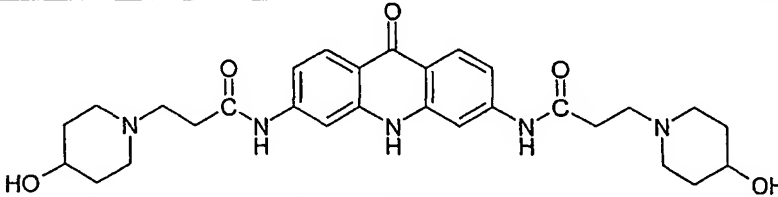
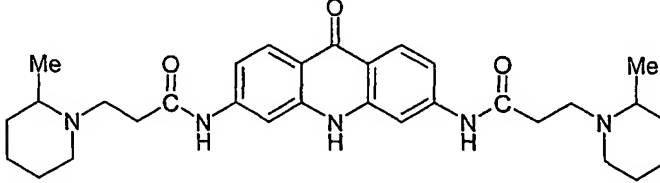
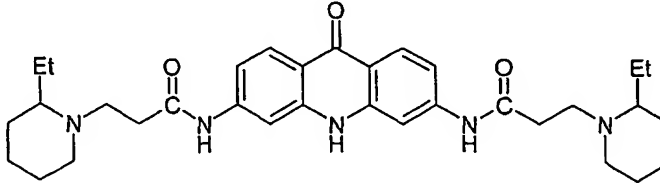
Class	# Free Base HCl Salt	Structure
3,6,9- ine	30 BSU-SB- 36/160 SB-ACI-13	
3,6,9- ine	31 BSU-SB- 36/164 SB-ACI-14	
3,6,9- ine	32 JC-ACI-3A JC-ACI-3	
3,6,9- ine	33 JC-ACI-4A JC-ACI-4	
3,6,9- ine	34 JC-ACI-5A JC-ACI-5	

- 36 -

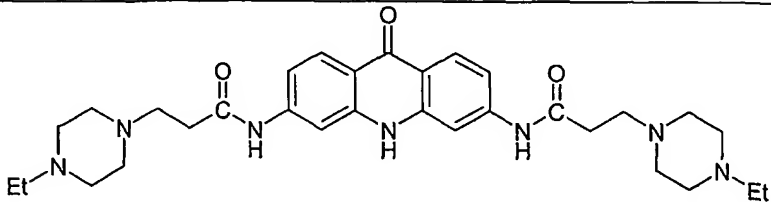
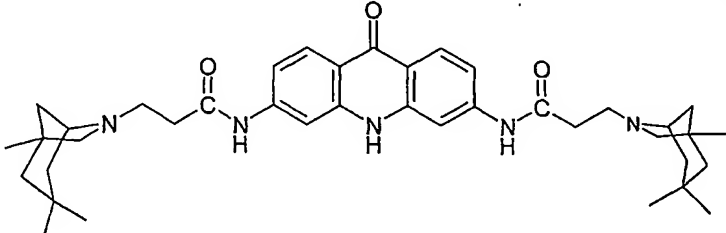
Class	# Free Base HCl Salt	Structure
3,6,9- ine	35 JC-ACI-9A JC-ACI-9	
3,6,9- ine	36 JH-ACI-100 JH-ACI-101	
3,6,9- ine	37 JH-ACI-102 JH-ACI-103	
3,6,9- ine	38 JH-ACI-64 JH-ACI-65	

Class	# Free Base HCl Salt	Structure
3,6,9- ine	39 JH-ACI-68 JH-ACI-69	
3,6,9- ine	40 JH-ACI-73 JH-ACI-74	
3,6,9- ine	41 JH-ACI-75 JH-ACI-76	
3,6,9- ine	42 JH-ACI-77 JH-ACI-78	
3,6,9- ine	43 JH-ACI-81 JH-ACI-82	

Class	# Free Base HCl Salt	Structure
3,6,9- ine	44 JH-ACI-85 JH-ACI-86	
3,6,9- ine	45 JH-ACI-87 JH-ACI-88	
3,6,9- ine	46 JH-ACI-89 JH-ACI-90	
3,6,9- ine	47 JM-ACI-13 JM-ACI-14	
3,6- one	48 BR-ACO-11 BR-ACO-6	
3,6- one	49 BR-ACO-12 BR-ACO-7	

Class	# Free Base HCl Salt	Structure
3,6-one	50 BR-ACO-13 BR-ACO-8	
3,6-one	51 BR-ACO-14 BR-ACO-4	
3,6-one	52 BR-ACO-15 BR-ACO-5	
3,6-one	53 BR-ACO-23 BR-ACO-33	
3,6-one	54 BR-ACO-24 BR-ACO-34	
3,6-one	55 BR-ACO-26 BR-ACO-36	
3,6-one	56 BR-ACO-27 BR-ACO-37	

- 40 -

Class	# Free Base HCl Salt	Structure
3,6-one	57 BR-ACO-29 BR-ACO-39	
3,6-one	58 JH-ACO-31 JH-ACO-32	

Chemical Terms

The term "carbo," "carbyl," "hydrocarbo," and "hydrocarbyl," as used herein, pertain
 5 to compounds and/or groups which have only carbon and hydrogen atoms.

The term "hetero," as used herein, pertains to compounds and/or groups which
 have at least one heteroatom, for example, multivalent heteroatoms (which are also
 suitable as ring heteroatoms) such as boron, silicon, nitrogen, phosphorus, oxygen,
 10 and sulfur, and monovalent heteroatoms, such as fluorine, chlorine, bromine, and
 iodine.

The term "saturated," as used herein, pertains to compounds and/or groups which
 do not have any carbon-carbon double bonds or carbon-carbon triple bonds.

15

The term "unsaturated," as used herein, pertains to compounds and/or groups
 which have at least one carbon-carbon double bond or carbon-carbon triple bond.

The term "aliphatic," as used herein, pertains to compounds and/or groups which
 20 are linear or branched, but not cyclic (also known as "acyclic" or "open-chain"
 groups).

- 41 -

The term "cyclic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., spiro, fused, bridged).

5 The term "ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms.

10 The term "aromatic ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 5 to 8 covalently linked atoms, which ring is aromatic.

The term "heterocyclic ring," as used herein, pertains to a closed ring of from 3 to 10 covalently linked atoms, more preferably 3 to 8 covalently linked atoms, wherein at least one of the ring atoms is a multivalent ring heteroatom, for example, nitrogen, phosphorus, silicon, oxygen, and sulfur, though more commonly nitrogen, 15 oxygen, and sulfur.

The term "alicyclic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., spiro, fused, bridged), wherein said ring(s) are not aromatic.

20 The term "aromatic," as used herein, pertains to compounds and/or groups which have one ring, or two or more rings (e.g., fused), wherein said ring(s) are aromatic.

The term "heterocyclic," as used herein, pertains to cyclic compounds and/or groups which have one heterocyclic ring, or two or more heterocyclic rings (e.g., 25 spiro, fused, bridged), wherein said ring(s) may be alicyclic or aromatic.

The term "heteroaromatic," as used herein, pertains to cyclic compounds and/or groups which have one heterocyclic ring, or two or more heterocyclic rings (e.g., fused), wherein said ring(s) is aromatic.

30

- 42 -

Substituents

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

5

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

10

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from: halo; hydroxy; ether (e.g., C₁₋₇alkoxy); formyl; acyl (e.g., C₁₋₇alkylacyl, C₅₋₂₀arylacyl); acylhalide; carboxy; ester; acyloxy; amido; acylamido; thioamido; tetrazolyl; amino; nitro; nitroso; azido; cyano; isocyano; cyanato; isocyanato; thiocyno; isothiocyano; sulfhydryl; thioether (e.g., C₁₋₇alkylthio); sulfonic acid; sulfonate; sulfone; sulfonyloxy; sulfinyloxy; sulfamino; sulfonamino; sulfinamino; sulfamyl; sulfonamido; C₁₋₇alkyl (including, e.g., C₁₋₇haloalkyl, C₁₋₇hydroxyalkyl, C₁₋₇carboxyalkyl, C₁₋₇aminoalkyl, C₅₋₂₀aryl-C₁₋₇alkyl); C₃₋₂₀heterocyclyl; or C₅₋₂₀aryl (including, e.g., C₅₋₂₀carboaryl, C₅₋₂₀heteroaryl, C₁₋₇alkyl-C₅₋₂₀aryl and C₅₋₂₀haloaryl)).

15

20

In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from:

25

-F, -Cl, -Br, and -I;
-OH;
-OMe, -OEt, -O(tBu), and -OCH₂Ph;
-SH;
-SMe, -SEt, -S(tBu), and -SCH₂Ph;
-C(=O)H;
-C(=O)Me, -C(=O)Et, -C(=O)(tBu), and -C(=O)Ph;

30

- 43 -

- C(=O)OH;
- C(=O)OMe, -C(=O)OEt, and -C(=O)O(tBu);
- C(=O)NH₂, -C(=O)NHMe, -C(=O)NMe₂, and -C(=O)NHET;
- NHC(=O)Me, -NHC(=O)Et, -NHC(=O)Ph, succinimidyl, and maleimidyl;
- 5 -NH₂, -NHMe, -NHET, -NH(iPr), -NH(nPr), -NMe₂, -NEt₂, -N(iPr)₂, -N(nPr)₂, -N(nBu)₂,
and -N(tBu)₂;
- CN;
- NO₂;
- Me, -Et, -nPr, -iPr, -nBu, -tBu;
- 10 -CF₃, -CHF₂, -CH₂F, -CCl₃, -CBr₃, -CH₂CH₂F, -CH₂CHF₂, and -CH₂CF₃;
- OCF₃, -OCHF₂, -OCH₂F, -OCCl₃, -OCBr₃, -OCH₂CH₂F, -OCH₂CHF₂, and
-OCH₂CF₃;
- CH₂OH, -CH₂CH₂OH, and -CH(OH)CH₂OH;
- CH₂NH₂, -CH₂CH₂NH₂, and -CH₂CH₂NMe₂; and,
- 15 optionally substituted phenyl.

- In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -CONH₂, -CONHMe, -NH₂, -NMe₂, -NEt₂,
- 20 -N(nPr)₂, -N(iPr)₂, -CN, -NO₂, -Me, -Et, -CF₃, -OCF₃, -CH₂OH, -CH₂CH₂OH, -CH₂NH₂, -CH₂CH₂NH₂, and -Ph.

- In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from: hydroxy; ether (e.g., C₁₋₇alkoxy); ester; amido; amino;
- 25 and, C₁₋₇alkyl (including, e.g., C₁₋₇haloalkyl, C₁₋₇hydroxyalkyl, C₁₋₇carboxyalkyl, C₁₋₇aminoalkyl, C₅₋₂₀aryl-C₁₋₇alkyl).

- In one preferred embodiment, the substituent(s), often referred to herein as R, are independently selected from:
- 30 -OH;
- OMe, -OEt, -O(tBu), and -OCH₂Ph;
- C(=O)OMe, -C(=O)OEt, and -C(=O)O(tBu);
- C(=O)NH₂, -C(=O)NHMe, -C(=O)NMe₂, and -C(=O)NHET;

- 44 -

-NH₂, -NHMe, -NHEt, -NH(iPr), -NH(nPr), -NMe₂, -NEt₂, -N(iPr)₂, -N(nPr)₂, -N(nBu)₂, and -N(tBu)₂;

-Me, -Et, -nPr, -iPr, -nBu, -tBu;

-CF₃, -CHF₂, -CH₂F, -CCl₃, -CBr₃, -CH₂CH₂F, -CH₂CHF₂, and -CH₂CF₃;

5 -CH₂OH, -CH₂CH₂OH, and -CH(OH)CH₂OH; and,

-CH₂NH₂, -CH₂CH₂NH₂, and -CH₂CH₂NMe₂.

The substituents are described in more detail below.

10 C₁₋₇alkyl: The term "C₁₋₇alkyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a C₁₋₇hydrocarbon compound having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, or a combination thereof, and which may be saturated, partially unsaturated, or fully unsaturated.

15 Examples of (unsubstituted) saturated linear C₁₋₇alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, and n-pentyl (amyl).

Examples of (unsubstituted) saturated branched C₁₋₇alkyl groups include, but are not limited to, iso-propyl, iso-butyl, sec-butyl, tert-butyl, and neo-pentyl.

20

Examples of saturated alicyclic (carbocyclic) C₁₋₇alkyl groups (also referred to as "C₃₋₇cycloalkyl" groups) include, but are not limited to, unsubstituted groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, as well as substituted groups (e.g., groups which comprise such groups), such as methylcyclopropyl,

25 dimethylcyclopropyl, methylcyclobutyl, dimethylcyclobutyl, methylcyclopentyl, dimethylcyclopentyl, methylcyclohexyl, dimethylcyclohexyl, cyclopropylmethyl and cyclohexylmethyl.

30 Examples of (unsubstituted) unsaturated C₁₋₇alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C₂₋₇alkenyl" groups) include, but are not limited to, ethenyl (vinyl, -CH=CH₂), 2-propenyl (allyl, -CH=CH-CH₂), isopropenyl (-C(CH₃)=CH₂), butenyl, pentenyl, and hexenyl.

- 45 -

Examples of (unsubstituted) unsaturated C₁₋₇alkyl groups which have one or more carbon-carbon triple bonds (also referred to as "C₂₋₇alkynyl" groups) include, but are not limited to, ethynyl (ethynyl) and 2-propynyl (propargyl).

- 5 Examples of unsaturated alicyclic (carbocyclic) C₁₋₇alkyl groups which have one or more carbon-carbon double bonds (also referred to as "C₃₋₇cycloalkenyl" groups) include, but are not limited to, unsubstituted groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl, as well as substituted groups (e.g., groups which comprise such groups) such as cyclopropenylmethyl and
10 cyclohexenylmethyl.

C₃₋₂₀heterocyclyl: The term "C₃₋₂₀heterocyclyl," as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a C₃₋₂₀heterocyclic compound, said compound having one ring, or two or more rings
15 (e.g., spiro, fused, bridged), and having from 3 to 20 ring atoms, atoms, of which from 1 to 10 are ring heteroatoms, and wherein at least one of said ring(s) is a heterocyclic ring. Preferably, each ring has from 3 to 7 ring atoms, of which from 1 to 4 are ring heteroatoms. "C₃₋₂₀" denotes ring atoms, whether carbon atoms or heteroatoms.

20

Examples of (non-aromatic) monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N₁: aziridine (C₃), azetidine (C₄), pyrrolidine (tetrahydropyrrole) (C₅), pyrroline (e.g.,
25 3-pyrroline, 2,5-dihydropyrrole) (C₅), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C₅), piperidine (C₆), dihydropyridine (C₆), tetrahydropyridine (C₆), azepine (C₇);

O₁: oxirane (C₃), oxetane (C₄), oxolane (tetrahydrofuran) (C₅), oxole (dihydrofuran) (C₅), oxane (tetrahydropyran) (C₆), dihydropyran (C₆), pyran (C₆), oxepin (C₇);

30

S₁: thiirane (C₃), thietane (C₄), thiolane (tetrahydrothiophene) (C₅), thiane (tetrahydrothiopyran) (C₆), thiepane (C₇);

- 46 -

O₂: dioxolane (C₅), dioxane (C₆), and dioxepane (C₇);

O₃: trioxane (C₆);

- 5 N₂: imidazolidine (C₅), pyrazolidine (diazolidine) (C₅), imidazoline (C₅), pyrazoline (dihydropyrazole) (C₅), piperazine (C₆);

- N₁O₁: tetrahydrooxazole (C₅), dihydrooxazole (C₅), tetrahydroisoxazole (C₅), dihydroisoxazole (C₅), morpholine (C₆), tetrahydrooxazine (C₆), dihydrooxazine
10 (C₆), oxazine (C₆);

N₁S₁: thiazoline (C₅), thiazolidine (C₅), thiomorpholine (C₆);

- N₂O₁: oxadiazine (C₆);
15

O₁S₁: oxathiole (C₅) and oxathiane (thioxane) (C₆); and,

N₁O₁S₁: oxathiazine (C₆).

- 20 Examples of substituted (non-aromatic) monocyclic heterocyclyl groups include saccharides, in cyclic form, for example, furanoses (C₅), such as arabinofuranose, lyxofuranose, ribofuranose, and xylofuranse, and pyranoses (C₆), such as allopyranose, altropyranose, glucopyranose, mannopyranose, gulopyranose, idopyranose, galactopyranose, and talopyranose.

25

Examples of heterocyclyl groups which are also heteroaryl groups are described below with aryl groups.

- C₅₋₂₀aryl: The term "C₅₋₂₀aryl," as used herein, pertains to a monovalent moiety
30 obtained by removing a hydrogen atom from an aromatic ring atom of a C₅₋₂₀aromatic compound, said compound having one ring, or two or more rings (e.g., fused), and having from 5 to 20 ring atoms, and wherein at least one of said ring(s) is an aromatic ring. Preferably, each ring has from 5 to 7 ring atoms.

- 47 -

In this context, the prefixes (e.g., C₃₋₂₀, C₅₋₇, C₅₋₆, etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C₅₋₆aryl," as used herein, pertains to an aryl group having 5
5 or 6 ring atoms. Examples of groups of aryl groups include C₃₋₂₀aryl, C₅₋₇aryl, C₅₋₆aryl.

- The ring atoms may be all carbon atoms, as in "carboaryl groups" (e.g., C₅₋₂₀carboaryl).
- 10 Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e., phenyl) (C₆), naphthalene (C₁₀), azulene (C₁₀), anthracene (C₁₄), phenanthrene (C₁₄), naphthacene (C₁₈), and pyrene (C₁₆).
- 15 Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C₉), isoindene (C₉), and fluorene (C₁₃).

Alternatively, the ring atoms may include one or more heteroatoms, including but
20 not limited to oxygen, nitrogen, and sulfur, as in "heteroaryl groups." In this case, the group may conveniently be referred to as a "C₅₋₂₀heteroaryl" group, wherein "C₅₋₂₀" denotes ring atoms, whether carbon atoms or heteroatoms. Preferably, each ring has from 5 to 7 ring atoms, of which from 0 to 4 are ring heteroatoms.

25 Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

- N₁: pyrrole (azole) (C₅), pyridine (azine) (C₆);
O₁: furan (oxole) (C₅);
S₁: thiophene (thiole) (C₅);
30 N₁O₁: oxazole (C₅), isoxazole (C₅), isoxazine (C₆);
N₂O₁: oxadiazole (furazan) (C₅);
N₃O₁: oxatriazole (C₅);
N₁S₁: thiazole (C₅), isothiazole (C₅);

- 48 -

N₂: imidazole (1,3-diazole) (C₅), pyrazole (1,2-diazole) (C₅), pyridazine (1,2-diazine) (C₆), pyrimidine (1,3-diazine) (C₆) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C₆);

N₃: triazole (C₅), triazine (C₆); and,

5 N₄: tetrazole (C₅).

Examples of heterocyclic groups (some of which are also heteroaryl groups) which comprise fused rings, include, but are not limited to:

C₉heterocyclic groups (with 2 fused rings) derived from benzofuran (O₁),
 10 isobenzofuran (O₁), indole (N₁), isoindole (N₁), purine (N₄) (e.g., adenine, guanine), benzimidazole (N₂), benzoxazole (N₁O₁), benzisoxazole (N₁O₁), benzodioxole (O₂), benzofurazan (N₂O₁), benzotriazole (N₃), benzothiofuran (S₁), benzothiazole (N₁S₁), benzothiadiazole (N₂S);

C₁₀heterocyclic groups (with 2 fused rings) derived from benzodioxan (O₂),
 15 quinoline (N₁), isoquinoline (N₁), benzoxazine (N₁O₁), benzodiazine (N₂), pyridopyridine (N₂), quinoxaline (N₂), quinazoline (N₂);

C₁₃heterocyclic groups (with 3 fused rings) derived from carbazole (N₁), dibenzofuran (O₁), dibenzothiophene (S₁); and,

C₁₄heterocyclic groups (with 3 fused rings) derived from acridine (N₁),
 20 xanthene (O₁), phenoxathiin (O₁S₁), phenazine (N₂), phenoxazine (N₁O₁), phenothiazine (N₁S₁), thianthrene (S₂), phenanthridine (N₁), phenanthroline (N₂), phenazine (N₂).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom
 25 in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methylpyrrole. Examples of N-substituent include, but are not limited to C₁₋₇alkyl, C₃₋₂₀heterocyclyl, C₅₋₂₀aryl, and acyl groups.

30 Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as -N(→O)= (also denoted -N⁺(→O⁻)=). For example, quinoline may be substituted to

- 49 -

give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon
5 atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

- C₅: cyclopentanone, cyclopentenone, cyclopentadienone;
C₆: cyclohexanone, cyclohexenone, cyclohexadienone;
10 O₁: furanone (C₅), pyrone (C₆);
N₁: pyrrolidone (pyrrolidinone) (C₅), piperidinone (piperidone) (C₆), piperidinedione (C₆);
N₂: imidazolidone (imidazolidinone) (C₅), pyrazolone (pyrazolinone) (C₅),
piperazinone (C₆), piperazinedione (C₆), pyridazinone (C₆), pyrimidinone (C₆)
15 (e.g., cytosine), pyrimidinedione (C₆) (e.g., thymine, uracil), barbituric acid (C₆);
N₁S₁: thiazolone (C₅), isothiazolone (C₅);
N₁O₁: oxazolinone (C₅).

Polycyclic examples of such groups include, but are not limited to, those derived
20 from:

- C₉: indenedione;
N₁: oxindole (C₉);
O₁: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C₁₀);
N₁O₁: benzoxazolinone (C₉), benzoxazolinone (C₁₀);
25 N₂: quinazolinone (C₁₀);
N₄: purinone (C₉) (e.g., guanine).

- Still more examples of cyclic groups which bear one or more oxo (=O) groups on
ring carbon atoms include, but are not limited to, those derived from:
30 cyclic anhydrides (-C(=O)-O-C(=O)- in a ring), including but not limited to
maleic anhydride (C₅), succinic anhydride (C₅), and glutaric anhydride (C₆);
cyclic carbonates (-O-C(=O)-O- in a ring), such as ethylene carbonate (C₅)
and 1,2-propylene carbonate (C₅);

- 50 -

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C₅), maleimide (C₅), phthalimide, and glutarimide (C₆);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β -propiolactone, γ -butyrolactone, δ -valerolactone (2-piperidone), and

5 ϵ -caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β -propiolactam (C₄), γ -butyrolactam (2-pyrrolidone) (C₅), δ -valerolactam (C₆), and ϵ -caprolactam (C₇);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C₅);

10 cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C₅) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C₆).

The above C₁₋₇alkyl, C₃₋₂₀heterocyclyl, and C₅₋₂₀aryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below.

15 Hydrogen: -H. Note that if the substituent at a particular position is hydrogen, it may be convenient to refer to the compound as being "unsubstituted" at that position.

20 Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C₁₋₇alkyl group (also referred to as a C₁₋₇alkoxy group, discussed below), a C₃₋₂₀heterocyclyl group (also referred to as a C₃₋₂₀heterocycloxy group), or a C₅₋₂₀aryl group (also referred to as a C₅₋₂₀aryloxy group), preferably a C₁₋₇alkyl group.

C₁₋₇alkoxy: -OR, wherein R is a C₁₋₇alkyl group. Examples of C₁₋₇alkoxy groups include, but are not limited to, -OCH₃ (methoxy), -OCH₂CH₃ (ethoxy) and -OC(CH₃)₃ (tert-butoxy).

30

- 51 -

Oxo (keto, -one): =O. Examples of cyclic compounds and/or groups having, as a substituent, an oxo group (=O) include, but are not limited to, carbocyclics such as cyclopentanone and cyclohexanone; heterocyclics, such as pyrone, pyrrolidone, pyrazolone, pyrazolinone, piperidone, piperidinedione, piperazinedione, and
5 imidazolidone; cyclic anhydrides, including but not limited to maleic anhydride and succinic anhydride; cyclic carbonates, such as propylene carbonate; imides, including but not limited to, succinimide and maleimide; lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β -propiolactone, γ -butyrolactone, δ -valerolactone, and ϵ -caprolactone; and lactams (cyclic amides, -NH-C(=O)- in a
10 ring), including, but not limited to, β -propiolactam, γ -butyrolactam, δ -valerolactam, and ϵ -caprolactam.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably hydrogen
15 or a C₁₋₇alkyl group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

20 Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C₁₋₇alkyl group (also referred to as C₁₋₇alkylacyl or C₁₋₇alkanoyl), a C₃₋₂₀heterocyclyl group (also referred to as C₃₋₂₀heterocyclylacyl), or a C₅₋₂₀aryl group (also referred to as C₅₋₂₀arylacyl), preferably a C₁₋₇alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH₃ (acetyl), -C(=O)CH₂CH₃ (propionyl), -C(=O)C(CH₃)₃
25 (butyryl), and -C(=O)Ph (benzoyl, phenone).

Acylhalide (haloformyl, halocarbonyl): -C(=O)X, wherein X is -F, -Cl, -Br, or -I, preferably -Cl, -Br, or -I.

30 Carboxy (carboxylic acid): -COOH.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a

- 52 -

C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of ester groups include, but are not limited to, -C(=O)OCH₃, -C(=O)OCH₂CH₃, -C(=O)OC(CH₃)₃, and -C(=O)OPh.

- 5 Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of acyloxy groups include, but are not limited to, -OC(=O)CH₃ (acetoxy), -OC(=O)CH₂CH₃, -OC(=O)C(CH₃)₃, -OC(=O)Ph, and -OC(=O)CH₂Ph.

10

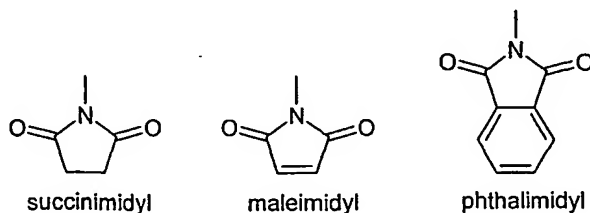
Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): -C(=O)NR¹R², wherein R¹ and R² are independently amino substituents, as defined for amino groups.

Examples of amido groups include, but are not limited to, -C(=O)NH₂,

-C(=O)NHCH₃, -C(=O)NH(CH₃)₂, -C(=O)NHCH₂CH₃, and -C(=O)N(CH₂CH₃)₂, as

- 15 well as amido groups in which R¹ and R², together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

- 20 Acylamido (acylamino): -NR¹C(=O)R², wherein R¹ is an amide substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group, and R² is an acyl substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of acylamide groups include, but are not limited to, -NHC(=O)CH₃,
 25 -NHC(=O)CH₂CH₃, and -NHC(=O)Ph. R¹ and R² may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:

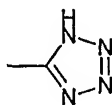


- 53 -

Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)NH(CH_3)_2$, and $-C(=S)NHCH_2CH_3$.

5

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



- 10 Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di- C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having
- 15 from 4 to 8 ring atoms. Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHCH(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and $-NHPh$. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, piperidino, piperazino, morpholino, and thiomorpholino.

20 Nitro: $-NO_2$.

Nitroso: $-NO$.

Azido: $-N_3$.

25

Cyano (nitrile, carbonitrile): $-CN$.

Isocyano: $-NC$.

30 Cyanato: $-OCN$.

- 54 -

Isocyanato: -NCO.

Thiocyano (thiocyanato): -SCN.

5 Isothiocyano (isothiocyanato): -NCS.

Sulphydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a
10 C₁₋₇alkyl group (also referred to as a C₁₋₇alkylthio group), a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of C₁₋₇alkylthio groups include, but are not limited to, -SCH₃ and -SCH₂CH₃.

Sulfonic acid (sulfo): -S(=O)₂OH.

15

Sulfonate (sulfonic acid ester): -S(=O)₂OR, wherein R is a sulfonate substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of sulfonate groups include, but are not limited to, -S(=O)₂OCH₃ and -S(=O)₂OCH₂CH₃.

20

Sulfone (sulfonyl): -S(=O)₂R, wherein R is a sulfone substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of sulfone groups include, but are not limited to, -S(=O)₂CH₃ (methanesulfonyl, mesyl), -S(=O)₂CF₃, -S(=O)₂CH₂CH₃, and 4-

25

methylphenylsulfonyl (tosyl).

Sulfonyloxy: -OS(=O)₂R, wherein R is a sulfonyloxy substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl group. Examples of sulfonyloxy groups include, but are not limited to,

30

-OS(=O)₂CH₃ and -OS(=O)₂CH₂CH₃.

Sulfinyloxy: -OS(=O)R, wherein R is a sulfinyloxy substituent, for example, a C₁₋₇alkyl group, a C₃₋₂₀heterocyclyl group, or a C₅₋₂₀aryl group, preferably a C₁₋₇alkyl

- 55 -

group. Examples of sulfinyloxy groups include, but are not limited to, $-\text{OS}(=\text{O})\text{CH}_3$ and $-\text{OS}(=\text{O})\text{CH}_2\text{CH}_3$.

Sulfamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{OH}$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-\text{NHS}(=\text{O})_2\text{OH}$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{OH}$.

Sulfonamino: $-\text{NR}^1\text{S}(=\text{O})_2\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-\text{NHS}(=\text{O})_2\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})_2\text{C}_6\text{H}_5$.

Sulfinamino: $-\text{NR}^1\text{S}(=\text{O})\text{R}$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinamino groups include, but are not limited to, $-\text{NHS}(=\text{O})\text{CH}_3$ and $-\text{N}(\text{CH}_3)\text{S}(=\text{O})\text{C}_6\text{H}_5$.

Sulfamyl: $-\text{S}(=\text{O})\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-\text{S}(=\text{O})\text{NH}_2$, $-\text{S}(=\text{O})\text{NH}(\text{CH}_3)$, $-\text{S}(=\text{O})\text{N}(\text{CH}_3)_2$, $-\text{S}(=\text{O})\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{S}(=\text{O})\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{S}(=\text{O})\text{NHPh}$.

Sulfonamido: $-\text{S}(=\text{O})_2\text{NR}^1\text{R}^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-\text{S}(=\text{O})_2\text{NH}_2$, $-\text{S}(=\text{O})_2\text{NH}(\text{CH}_3)$, $-\text{S}(=\text{O})_2\text{N}(\text{CH}_3)_2$, $-\text{S}(=\text{O})_2\text{NH}(\text{CH}_2\text{CH}_3)$, $-\text{S}(=\text{O})_2\text{N}(\text{CH}_2\text{CH}_3)_2$, and $-\text{S}(=\text{O})_2\text{NHPh}$.

As mentioned above, a C_{1-7} alkyl group may be substituted with, for example, hydroxy (also referred to as a C_{1-7} hydroxyalkyl group), C_{1-7} alkoxy (also referred to as a C_{1-7} alkoxyalkyl group), amino (also referred to as a C_{1-7} aminoalkyl group), halo (also referred to as a C_{1-7} haloalkyl group), carboxy (also referred to as a

- 56 -

C₁₋₇carboxyalkyl group), and C₅₋₂₀aryl (also referred to as a C₅₋₂₀aryl-C₁₋₇alkyl group).

Similarly, a C₅₋₂₀aryl group may be substituted with, for example, hydroxy (also referred to as a C₅₋₂₀hydroxyaryl group), halo (also referred to as a C₅₋₂₀haloaryl group), amino (also referred to as a C₅₋₂₀aminoaryl group, e.g., as in aniline), C₁₋₇alkyl (also referred to as a C₁₋₇alkyl-C₅₋₂₀aryl group, e.g., as in toluene), and C₁₋₇alkoxy (also referred to as a C₁₋₇alkoxy-C₅₋₂₀aryl group, e.g., as in anisole).

10 These and other specific examples of such substituted groups are also discussed below.

C₁₋₇haloalkyl group: The term "C₁₋₇haloalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom (e.g., 1, 2, 3) has been replaced with a halogen atom (e.g., F, Cl, Br, I). If more than one hydrogen atom has been replaced with a halogen atom, the halogen atoms may independently be the same or different. Every hydrogen atom may be replaced with a halogen atom, in which case the group may conveniently be referred to as a C₁₋₇perhaloalkyl group." Examples of C₁₋₇haloalkyl groups include, but are not limited to, -CF₃,
15 -CHF₂, -CH₂F, -CCl₃, -CBr₃, -CH₂CH₂F, -CH₂CHF₂, and -CH₂CF₃.

C₁₋₇hydroxyalkyl: The term "C₁₋₇hydroxyalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom has been replaced with a hydroxy group. Examples of C₁₋₇hydroxyalkyl groups include, but are not limited to,
25 -CH₂OH, -CH₂CH₂OH, and -CH(OH)CH₂OH.

C₁₋₇carboxyalkyl: The term "C₁₋₇carboxyalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom has been replaced with a carboxy group. Examples of C₁₋₇carboxyalkyl groups include, but are not limited to,
30 -CH₂COOH and -CH₂CH₂COOH.

C₁₋₇aminoalkyl: The term "C₁₋₇aminoalkyl group," as used herein, pertains to a C₁₋₇alkyl group in which at least one hydrogen atom has been replaced with an

- 57 -

amino group. Examples of C₁₋₇aminoalkyl groups include, but are not limited to, -CH₂NH₂, -CH₂CH₂NH₂, and -CH₂CH₂N(CH₃)₂.

5 C₁₋₇alkyl-C₅₋₂₀aryl: The term "C₁₋₇alkyl-C₅₋₂₀aryl," as used herein, describes certain C₅₋₂₀aryl groups which have been substituted with a C₁₋₇alkyl group. Examples of such groups include, but are not limited to, tolyl (as in toluene), xylyl (as in xylene), mesityl (as in mesitylene), styryl (as in styrene), and cumenyl (as in cumene).

10 C₅₋₂₀aryl-C₁₋₇alkyl: The term "C₅₋₂₀aryl-C₁₋₇alkyl," as used herein, describes certain C₁₋₇alkyl groups which have been substituted with a C₅₋₂₀aryl group. Examples of such groups include, but are not limited to, benzyl (phenylmethyl), tolylmethyl, phenylethyl, and triphenylmethyl (trityl).

15 C₅₋₂₀haloaryl: The term "C₅₋₂₀haloaryl," as used herein, describes certain C₅₋₂₀aryl groups which have been substituted with one or more halo groups. Examples of such groups include, but are not limited to, halophenyl (e.g., fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl, whether ortho-, meta-, or para-substituted), dihalophenyl, trihalophenyl, tetrahalophenyl, and pentahalophenyl.

20 Other Forms

Included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form (-COO⁻), a salt or solvate thereof, as well as
25 conventional protected forms. Similarly, a reference to an amino group includes the protonated form (-N⁺HR¹R²), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form (-O⁻), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

- 58 -

Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr),
5 iso-propyl (iPr), n-butyl (nBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh), benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known
10 abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), isopropanol (iPrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et₂O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), 4-(dimethylamino)pyridine (DMAP), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

15

Isomers, Salts, Solvates, Protected Forms, and Prodrugs

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational,
20 or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r- forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations
25 thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

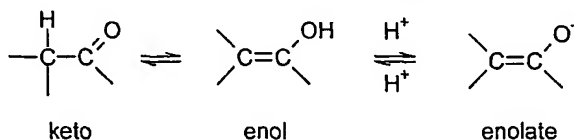
Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by
30 the position of atoms in space). For example, a reference to a methoxy group, -OCH₃, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, -CH₂OH. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl.

- 59 -

However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C₁₋₇alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

5

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, N-nitroso/hydroxyazo, and nitro/aci-nitro.



10

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ¹H, ²H (D), and ³H (T); C may be in any isotopic form, including ¹²C, ¹³C, and ¹⁴C; O may be in any isotopic form, including ¹⁶O and ¹⁸O; and the like.

15

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

20

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

25

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt.

- 60 -

Examples of pharmaceutically acceptable salts are discussed in Berge et al., 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{+3} . Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R_2^+ , NHR_3^+ , NR_4^+). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., -NH_2 may be -NH_3^+), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous. Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: acetic, propionic, succinic, glycolic, stearic, palmitic, lactic, malic, pantoic, tartaric, citric, gluconic, ascorbic, maleic, hydroxymaleic, phenylacetic, glutamic, aspartic, benzoic, cinnamic, pyruvic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and valeric. Examples of suitable polymeric anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be

- 61 -

conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active
5 compound in a chemically protected form. The term "chemically protected form,"
as used herein, pertains to a compound in which one or more reactive functional
groups are protected from undesirable chemical reactions, that is, are in the form of
a protected or protecting group (also known as a masked or masking group or a
blocked or blocking group). By protecting a reactive functional group, reactions
10 involving other unprotected reactive functional groups can be performed, without
affecting the protected group; the protecting group may be removed, usually in a
subsequent step, without substantially affecting the remainder of the molecule.
See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts,
Wiley, 1991).

15 For example, a hydroxy group may be protected as an ether (-OR) or an ester (-
OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl),
or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an
acetyl ester (-OC(=O)CH₃, -OAc).

20 For example, an aldehyde or ketone group may be protected as an acetal or ketal,
respectively, in which the carbonyl group (>C=O) is converted to a diether
(>C(OR)₂), by reaction with, for example, a primary alcohol. The aldehyde or
ketone group is readily regenerated by hydrolysis using a large excess of water in
25 the presence of acid.

For example, an amine group may be protected, for example, as an amide or a
urethane, for example, as: a methyl amide (-NHCO-CH₃); a benzyloxy amide
(-NHCO-OCH₂C₆H₅, -NH-Cbz); as a t-butoxy amide (-NHCO-OC(CH₃)₃, -NH-Boc);
30 a 2-biphenyl-2-propoxy amide (-NHCO-OC(CH₃)₂C₆H₄C₆H₅, -NH-Bpoc), as a
9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc),
as a 2-trimethylsilylethoxy amide (-NH-Teoc), as a 2,2,2-trichloroethoxy amide (-

- 62 -

NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases, as an N-oxide (>NO•).

For example, a carboxylic acid group may be protected as an ester for example, as:
5 an C₁₋₇alkyl ester (e.g., a methyl ester; a t-butyl ester); a C₁₋₇haloalkyl ester (e.g., a C₁₋₇trihaloalkyl ester); a triC₁₋₇alkylsilyl-C₁₋₇alkyl ester; or a C₅₋₂₀aryl-C₁₋₇alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

10 For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-CH₂NHC(=O)CH₃).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to
15 a compound which, when metabolised (e.g., *in vivo*), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

20 For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups (-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive
25 groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those wherein R is C₁₋₇alkyl (e.g., -Me, -Et); C₁₋₇aminoalkyl (e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl); and acyloxy-C₁₋₇alkyl (e.g., acyloxymethyl; acyloxyethyl; e.g., pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-
30 methyl)ethyl-carboxyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carboxyloxymethyl; 1-isopropoxy-carboxyloxyethyl; cyclohexyl-carboxyloxymethyl; 1-cyclohexyl-carboxyloxyethyl; cyclohexyloxy-carboxyloxymethyl; 1-cyclohexyloxy-

- 63 -

carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)carbonyloxyethyl).

5

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound. For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

10

Synthesis

The acridone and acridine compounds of the present invention may be prepared, for example, by the methods illustrated in Figures 1, 2, 3A, 3B, 4, 5, and 6, or by
15 adapting these or other well known methods in well known ways.

Figure 1 is a scheme illustrating a chemical synthesis method for certain 3,6-disubstituted acridones of the present invention. The reagents/conditions for the steps in Figure 1 are: (i) KNO_3 / H_2SO_4 ; (ii) CrO_3 , AcOH, reflux; (iii) SnCl_2 / HCl,
20 90-100°C; (iv) 3-chloropropionyl chloride (3-CPC), reflux; (v) NHR^1R^2 , EtOH, NaI, reflux; and, (vi) HCl. By using appropriate 1° or 2° amines, NHR^1R^2 , preferably 2° amines, different acridones of the present invention are obtained.

Figure 2 is a scheme illustrating a chemical synthesis method for certain 2,7-disubstituted acridones of the present invention. The reagents/conditions for the
25 steps in Figure 2 are: (i) Cu / CuSO_4 / K_2CO_3 / H_2O , 5 hrs reflux; (ii) polyphosphoric acid (PPA), 100°C, 5 hr; (iii) Na_2S , NaOH, EtOH, H_2O , reflux; (iv) 3-chloropropionyl chloride (3-CPC), reflux; (v) NHR^1R^2 , EtOH, NaI; and (vi) HCl. By using appropriate 1° or 2° amines, NHR^1R^2 , preferably 2° amines, different acridones of
30 the present invention are obtained.

Figure 3A is a scheme illustrating a chemical synthesis method for certain 2,6-disubstituted acridones of the present invention. The reagents/conditions for the

- 64 -

steps in Figure 3A are: (i) Cu, CuSO₄, K₂CO₃, H₂O; (ii) H₂SO₄, H₂O; (iii) Na₂S, NaOH; (iv) 3-chloroproponylchloride; (v) EtOH, KI, NHR¹R²; and, (vi) HCl. By using appropriate 1° or 2° amines, NHR¹R², preferably 2° amines, different acridones of the present invention are obtained.

5

Figure 3B is a scheme illustrating a chemical synthesis method for certain 2,6-disubstituted acridones of the present invention. The reagents/conditions for the steps in Figure 3B are: (i) acetic anhydride, H₂O, Na₂CO₃; (ii) pentan-1-ol, KCO₃, Cu; (iii) H₂SO₄, H₂O; (iv) 3-chloroproponylchloride; (v) EtOH, KI, NHR¹R²; and, 10 (vi) HCl. By using appropriate 1° or 2° amines, NHR¹R², preferably 2° amines, different acridones of the present invention are obtained.

Figure 4 is a scheme illustrating a chemical synthesis method for certain 3,6,9-trisubstituted acridines of the present invention. The reagents/conditions for the 15 steps in Figure 4 are: (i) POCl₃, reflux; (ii) H₂N(PhR_m), CHCl₃, RT; and, (iii) NH₂(CH₂)_pNH₂, MeOH. By using appropriate 1° or 2° amines, NHR¹R², preferably 2° amines, and appropriate amines, Q-NHR^N (e.g., NH₂(CH₂)_pNH₂, substituted anilines, etc.), different acridines of the present invention are obtained.

20 Figure 5 is a scheme illustrating a chemical synthesis method for certain 2,7,9-trisubstituted acridines of the present invention. The reagents/conditions for the steps in Figure 5 are: (i) POCl₃, reflux; (ii) H₂N(PhR_m), CHCl₃, RT; and, (iii) NH₂(CH₂)_pNH₂, MeOH. By using appropriate 1° or 2° amines, NHR¹R², preferably 2° amines, and appropriate amines, Q-NHR^N (e.g., NH₂(CH₂)_pNH₂, 25 substituted anilines, etc.), different acridines of the present invention are obtained.

Figure 6 is a scheme illustrating a chemical synthesis method for certain 2,6,9-trisubstituted acridines of the present invention. The reagents/conditions for the steps in Figure 6 are: (i) POCl₃, reflux; (ii) H₂N(PhR_m), CHCl₃, RT; and, 30 (iii) NH₂(CH₂)_pNH₂, MeOH. By using appropriate 1° or 2° amines, NHR¹R², preferably 2° amines, and appropriate amines, Q-NHR^N (e.g., NH₂(CH₂)_pNH₂, substituted anilines, etc.), different acridines of the present invention are obtained.

- 65 -

Additional relevant synthesis methods are described in, for example, Matsumura, 1929 and Korolev et al., 1977, and the references cited therein.

Uses

5

The present invention provides active compounds, specifically, active acridines and acridones, as described herein. The term "active," as used herein, pertains to compounds which are capable of inhibiting telomerase and/or of regulating cell proliferation.

10

One of ordinary skill in the art is readily able to determine whether or not a candidate compound inhibits telomerase activity. For example, one assay which may conveniently be used in order to assess the telomerase inhibition offered by a particular compound is described in the examples below.

15

Thus, the present invention provides active compounds which inhibit telomerase, as well as methods of inhibiting telomerase, comprising contacting a cell with an effective amount of an active compound, preferably in the form of a pharmaceutically acceptable composition. Such a method may be practised *in vitro* or *in vivo*.

20

The present invention further provides active compounds which regulate cell proliferation, as well as methods of regulating cell proliferation, comprising contacting a cell with an effective amount of an active compound, preferably in the form of a pharmaceutically acceptable composition. Such a method may be practised *in vitro* or *in vivo*.

25

For example, a sample of cells (e.g., from a tumour) may be grown *in vitro* and an active compound brought into contact with said cells, and the effect of the compound on those cells observed. As examples of "effect," the morphological status of the cells may be determined, or the expression levels of genes associated with cell cycle regulation determined. Where the active compound is found to exert an influence on the cells, this may be used as a prognostic or diagnostic marker of

30

- 66 -

the efficacy of the compound in methods of treating a patient carrying cells of the same cellular type.

One of ordinary skill in the art is readily able to determine whether or not a
5 candidate compound regulates cell proliferation for any particular cell line. For example, one assay which may conveniently be used to assess the activity offered by a particular compound is described in the examples below.

The present invention further provides active compounds which are antiproliferative
10 agents. The term "antiproliferative agent" as used herein, pertain to a compound which treats a proliferative condition (i.e., a compound which is useful in the treatment of a proliferative condition).

One of ordinary skill in the art is readily able to determine whether or not a
15 candidate compound treats a proliferative condition for any particular cell line. For example, one assay which may conveniently be used to assess the activity offered by a particular compound is described in the examples below.

The terms "cell proliferation," "proliferative condition," "proliferative disorder," and
20 "proliferative disease," are used interchangeably herein and pertain to an unwanted or uncontrolled cellular proliferation of excessive or abnormal cells which is undesired, such as, neoplastic or hyperplastic growth, whether in vitro or in vivo. Examples of proliferative conditions include, but are not limited to, benign, pre-malignant, and malignant cellular proliferation, including but not limited to,
25 neoplasms and tumours (e.g., histocytoma, glioma, astrocyoma, osteoma), cancers (e.g., ovarian carcinoma, breast carcinoma, bowel cancer, colon cancer, renal cancer, lung cancer, small cell lung cancer, testicular cancer, prostate cancer, sarcoma, osteosarcoma, Kaposi's sarcoma, melanoma), leukemias, psoriasis, bone diseases, fibroproliferative disorders (e.g., of connective tissues), and
30 atherosclerosis. Any type of cell may be treated, including but not limited to, colon, kidney (renal), breast (mammary), lung, ovarian, liver (hepatic), pancreas, skin, and brain.

- 67 -

Antiproliferative compounds of the present invention have application in the treatment of cancer, and so the present invention further provides anticancer agents. The term "anticancer agent" as used herein, pertains to a compound which treats a cancer (i.e., a compound which is useful in the treatment of a cancer). The
5 anti-cancer effect may arise through one or more mechanisms, including but not limited to, the regulation of cell proliferation, the inhibition of angiogenesis (the formation of new blood vessels), the inhibition of metastasis (the spread of a tumour from its origin), the inhibition of invasion (the spread of tumour cells into neighbouring normal structures), or the promotion of apoptosis (programmed cell
10 death).

The invention further provides active compounds for use in a method of treatment of the human or animal body, for example, in the treatment of a proliferative condition, for example cancer. Such a method may comprise administering to such
15 a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in
20 veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included.

25 The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio.

30 The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited

- 68 -

to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

- 5 The invention further provides the use of an active compound for the manufacture of a medicament, for example, for the treatment of a proliferative condition.

The invention further provides a method of treatment of the human or animal body, the method comprising administering to a subject in need of treatment a
10 therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

Active compounds may also be used as cell culture additives to inhibit telomerase, for example, in order to regulate cell proliferation *in vitro*.

15

Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

- 20 Active compounds may also be used as a standard, for example, in an assay, in order to identify other active compounds, other telomerase inhibitors, other antiproliferative agents, etc.

Kits

25

One aspect of the invention pertains to a kit comprising (a) the active ingredient, preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, for example, written instructions on how to administer the active compound.

30

The written instructions may also include a list of indications for which the active ingredient is a suitable treatment.

- 69 -

Administration

- The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/ peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g., transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., an aerosol, e.g., through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot, for example, subcutaneously or intramuscularly.
- The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g., a guinea pig, a hamster, a rat, a mouse), murine (e.g., a mouse), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Formulations

- While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g., formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials well known to those skilled in the art and optionally other therapeutic agents.
- Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or

- 70 -

more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilisers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds,
5 materials, compositions, and/or dosage forms which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of a subject (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the
10 other ingredients of the formulation.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with the carrier
15 which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

20 Formulations may be in the form of liquids, solutions, suspensions, emulsions, tablets, lozenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, foams, lotions, oils, boluses, electuaries, or aerosols.

25 Formulations suitable for oral administration (e.g., by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a
30 paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a

- 71 -

suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g., povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g., sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g., transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include lozenges comprising the active compound in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e.,

- 72 -

by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active
5 compound.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment
10 base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures thereof. The
15 topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

20 When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat.
25 Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

30 Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active

- 73 -

compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g., by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised)

- 74 -

condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Formulations may be in the form of liposomes or other microparticulate systems
5 which are designed to target the active compound to blood components or one or more organs.

Dosage

10 It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors
15 including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will
20 ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect.

Administration *in vivo* can be effected in one dose, continuously or intermittently
25 throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by
30 the treating physician.

In general, a suitable dose of the active compound is in the range of about 0.1 to about 250 mg per kilogram body weight of the subject per day. Where the active

- 75 -

compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

5

EXAMPLES

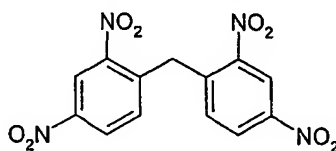
The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

10 General Procedures

Melting points (mp) were recorded on a Leica Galen III hot-stage melting point apparatus and are uncorrected. ¹H-NMR spectra were recorded at 250 MHz on a Bruker AC250 spectrometer in either d₆-Me₂SO or CDCl₃ solution at 303±1 K using Me₄Si (TMS) as internal standard. EI (70 eV), FAB and high resolution accurate mass spectra were determined by The School of Pharmacy (University of London, UK). Elemental analyses were carried out by Medac Ltd. (Brunel Science Center, Egham, Surrey, UK); results for elements indicated by symbols were within 0.4% of theoretical values. TLC was carried out on silica gel (Merck 60F-254) using CHCl₃/MeOH (0-20% MeOH) as eluent, with visualization at 254 and 366 nm. Organic solutions were dried over sodium sulphate.

Example 1

2,2',4,4'-Tetranitrodiphenylmethane (2)



25

Potassium nitrate (54.00 g, 0.53 mol) was added in portions to stirred concentrated H₂SO₄ (200 mL) whilst maintaining the temperature below 20°C. Diphenylmethane 1 (20.00 g, 0.12 mol) was added dropwise over 1.5 hr at 15°C to give a brown mixture. Upon complete addition the mixture was heated to 70°C for 40 min and produced a deep red solution. On cooling, the liquor was poured into ice and the

30

- 76 -

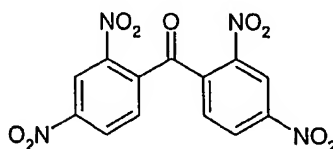
light brown solid produced collected. This solid was washed with H₂O (2 x 200 mL) and boiled with EtOH (300 mL) to afford the product **2** (33.83 g, 82%) as a cream solid.

- 5 Mp 170-173°C (lit. 173°C); ¹H-NMR (CDCl₃) δ 4.87 (s, 2H, CH₂), 7.41 (d, ³J = 8.5 Hz, 2H, H-6/6'), 8.44 (dd, ³J = 8.5 Hz, ⁴J = 2.4 Hz, 2H, H-5/5'), 8.97 (d, ⁴J = 2.4 Hz, 2H, H-3/3'); MS [EI] (relative intensity%) *m/z* 346 ([M]⁺, 41), 331 (48), 303 (57), 302 ([M-NO₂]⁺, 38), 300 (41), 268 (60), 285 (37), 256 ([M-N₂O₄]⁺, 19), 255 (29), 254 (64), 253 (24), 240 (32), 239 (100), 210 ([M-N₃O₆]⁺, 62), 193 (42), 164 ([M-N₄O₈]⁺, 46), 163 (80), C₁₃H₈N₄O₈ (M = 348.24) Found: C, 44.54; H, 2.38; N, 15.96%. requires C, 44.84; H, 2.31; N, 16.09%.

Example 2

2,2',4,4'-Tetranitrobenzophenone (**3**)

(BR-ACO-1)



15

To a refluxing solution of **2** (68.00 g, 0.20 mol) in glacial AcOH (100 mL) was slowly added CrO₃ (100.00 g, 1.00 mol) during 45 min, and the mixture refluxed for 3 hr. On cooling, the product was poured into water (3000 mL) and the resultant precipitate collected, washed with H₂O (2000 mL), EtOH (2 x 100 mL) and Et₂O (2 x 100 mL) to furnish the ketone **3** (66.40 g, 94%) as a cream solid.

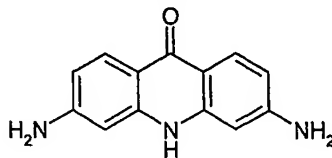
20

Mp 236-238°C (lit. 232°C; Matsumura, 1929); ¹H-NMR (d₆-DMSO) δ 8.03 (d, ³J = 2.0 Hz, 2H, H-6/6'), 8.65 (dd, ³J = 8.5 Hz, ⁴J = 2.1 Hz, 2H, H-5/5'), 8.96 (d, ⁴J = 2.1 Hz, 2H, H-3/3'); MS [EI] (relative intensity%) *m/z* 363 ([M+H]⁺, 6%), 346 ([M-O]⁺, 52), 316 ([M-NO₂]⁺, 100), 270 (28), 242 (16), 196 ([C₇H₄N₂O₅]⁺, 54), 195 ([C₇H₃N₂O₅]⁺, 100), 179 ([C₇H₄N₂O₄]⁺, 71), 149 ([C₇H₃NO₃]⁺, 85), 103 ([C₇H₃O]⁺, 82), 75 ([C₆H₃]⁺, 100). Found C, 43.13; H, 1.52; N, 15.38%, C₁₃H₆N₄O₉ (M = 362.22) requires C, 43.13; H, 1.52; N, 15.47%.

25

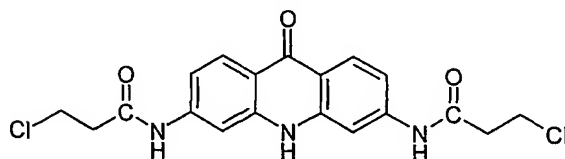
30

- 77 -

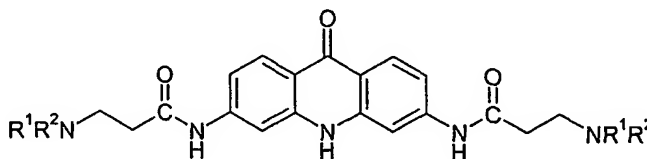
Example 33,6-Diamino-9(10*H*)-acridone (**4**)**(BR-ACO-2)**

- 5 Concentrated HCl (1.18 specific gravity, 300 mL) was added to anhydrous SnCl₂ (94.80 g, 0.50 mol) and the mixture heated to reflux (care, HCl gas evolved) to produce a clear solution. The ketone **3** (15.00g, 41.41 mmol) was added in portions over 30 min maintaining the temperature at 90-100°C. To the resultant suspension was added EtOH (25 mL) and concentrated HCl (30 mL) and reflux
- 10 continued for a further 3 hr. On cooling a further aliquot of HCl (50 mL) was added and the mixture left to stand for 18 hr. The resultant brown solid (hydrochloride salt) was collected and dried under air, this product was digested in hot dilute aq. HCl (0.1 M, 230 mL), refluxed with decolourising charcoal and filtered while hot. On cooling the solution was neutralised with aq NaOH (20% w/v, 150 mL) to pH
- 15 ~13 producing a light brown solid. This resultant mixture was heated to reflux for 20 min and filtered while hot. The residual solid was washed with 20% NaOH (50 mL) and hot H₂O until the filtrate achieved neutrality. The compound was dried *in vacuo* to furnish the acridone **4** (5.83 g, 62%) as a light brown solid.
- 20 Mp >300°C (lit. >300°C; Matsumura 1929); IR (KBr)/cm⁻¹ 3337 (N-H str.) 3214 (N-H str.) 1637, 1595, 1526, 1473: ¹H-NMR (d₆-DMSO) δ 5.86 (br s, 4H, D₂O exchanges, NH₂), 6.32 (d, ⁴J = 1.9 Hz, 2H, H-4/5), 6.39 (dd, ³J = 8.7 Hz, ⁴J = 1.9 Hz, 2H, H-2/7), 7.77 (d, ³J = 8.7 Hz, 2H, H-1/8), 10.57 (br s, 1H, D₂O exchanges, H-10); MS [EI] (relative intensity%) m/z 225 ([M]⁺, 100), 91 (65). Found C, 68.64; H, 4.82; N, 18.16%. C₁₃H₁₁N₃·0.1H₂O (M = 225.25) requires C, 68.77; H, 4.97; N, 18.51%.
- 25

- 78 -

Example 43,6-Bis(3-chloropropionamido)-9(10*H*)-acridone (**5**)
(BR-ACO-3)

- 5 A suspension of **4** (40.0 g, 0.178 mol), in 3-chloropropionyl chloride (3-CPC) (200 mL) was heated under reflux for 2 hr. The resultant mixture was cooled to 0°C then filtered, the collected product was washed with copious amounts of H₂O, EtOH (2 x 300 mL) and ether (2 x 200 mL), to provide the chloroamide **5** as a yellow solid (64.0 g, 88%), which was recrystallised from DMF-EtOH (5:1 v/v).
- 10 Mp > 300°C, ¹H-NMR (DMSO) δ 2.92 (4H, t, J 6.3 Hz, COCH₂CH₂Cl), 3.93 (4H, t, J 6.3 Hz, COCH₂CH₂Cl), 7.25 (2H, dd, J 1.8 Hz, J 8.8 Hz, H-2,7), 8.11 (2H, d, J 8.8 Hz, H-1,8), 8.14(2H, d, J 1.8 Hz, H-4,5), 10.54 (2H, s, NHCO), 11.76 (1H, s, H-10). m/z (EI) 406.0715 (C₁₉H₁₇N₃Cl₂ M+H requires 406.0725), found C 54.78; H 4.12; N 9.92% (anhydrous C₁₉H₁₇N₃Cl₂ 1.0 mol H₂O) Calcd C 54.95; H 4.37; N 10.12%.
- 15

Example 5General Aminolysis Procedure (**6**)

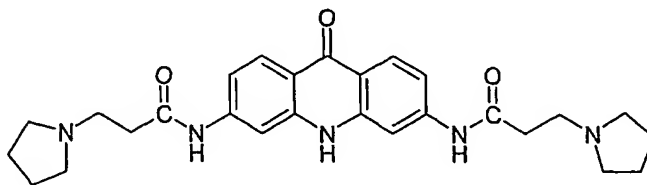
- 20 To a stirred refluxing suspension of **5** and NaI (0.3 g) in EtOH (70 mL) was added dropwise a suitable 2° amine, NHR¹R² (2.5 mL) in EtOH (15 mL). The mixture was stirred at reflux for a further 3 hr. After cooling the majority of EtOH was removed under vacuum and then filtered, the collected solid was dissolved in CHCl₃ (100 mL) and washed with dilute ammonia solution (2 x 75 mL), brine (100 mL),
- 25 dried and stirred over charcoal. The solvent was evaporated to produce a solid product. Recrystallisation EtOH / DMF provided the desired amine, **6**.

- 79 -

The acid addition salts of these amine derivatives, **7**, were prepared to increase solubility for biological evaluation.

Example 6

5 3,6-Bis[3-(pyrrolidino)propionamido]-9(10*H*)-acridone
 (BR-ACO-14)



Chloroamide **5** (1.0 g, 2.5 mmol) was treated with pyrrolidine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-14** (0.71 g, 10 61%) as a yellow solid.

Mp > 320°C, NMR (DMSO) δ 1.69 (8H, m, N(CH₂CH₂)₂), 2.50 (8H, m, N(CH₂CH₂)₂), 2.55 (4H, t, J 7.1 Hz, COCH₂CH₂N), 2.75 (4H, t, J 7.1 Hz, COCH₂CH₂N), 7.15 (2H, dd, J 1.7 Hz, J 8.8 Hz, H-2,7), 8.07 (2H, d, J 8.7 Hz, H-1,8), 8.11 (2H, d, J 1.7 Hz, H-4,5), 10.47 (2H, s, NHCO), 11.62 (1H, s, H-10), m/z 15 (EI) 476.2654 (C₂₇H₃₄N₅O₃ M+H requires 476.2662), found C 65.80; H 6.80; N 14.19%, Calcd (anhydrous C₂₇H₃₄N₅O₃·1.0 mol H₂O) C 65.70; H 7.15; N 14.19%.

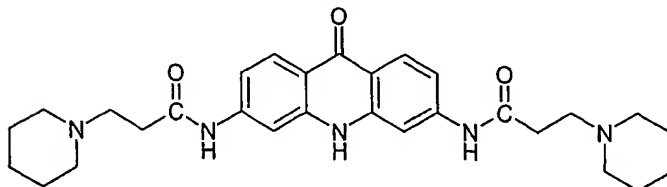
Example 7

20 Dihydrochloride Salt
 (BR-ACO-4)

The dihydrochloride addition salt, **BR-ACO-4**, of the compound in the previous example, was also prepared by treatment with HCl.

25

- 80 -

Example 83,6-Bis[3-(piperidino)propionamido]-9(10*H*)-acridone
(**BR-ACO-15**)

- 5 Chloroamide **5** (1.0 g, 2.5 mmol) was treated with piperidine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-15** (0.81 g, 60%) as a yellow solid.

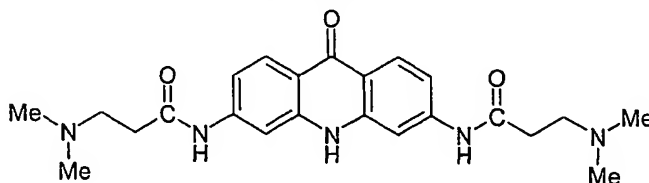
- Mp > 320°C ¹H-NMR (CDCl₃) δ 1.61 (4H, m, N(CH₂CH₂)CH₂), 1.77 (8H, m, N(CH₂CH₂)CH₂), 2.61 (8H, m, N(CH₂CH₂)₂), 2.65 (4H, t, J 5.5 Hz, COCH₂CH₂N), 2.74 (4H, t, J 5.5 Hz, COCH₂CH₂N), 6.84 (2H, dd, J 1.9 Hz, J 8.7 Hz, H-2,7), 8.29 (2H, d, J 1.9 Hz, H-4,5), 8.37 (2H, d, J 8.7 Hz, H-1,8), 9.02 (1H, s, H-10) 11.77 (2H, s, NHCO), m/z (EI) 504.2974 (C₂₉H₃₈N₅O₃ M+H requires 504.2975), found C 64.47; H 7.56; N 12.83%, Calcd (anhydrous C₂₉H₃₇N₅O₃·2.0 mol H₂O) C 64.54; H 7.66; N 12.98%.

Example 9Dihydrochloride Salt
(**BR-ACO-5**)

20

The dihydrochloride addition salt, **BR-ACO-5**, of the compound in the previous example, was also prepared by treatment with HCl.

- 81 -

Example 103,6-Bis[3-(dimethylamino)propionamido]-9(10*H*)-acridone**(BR-ACO-11)**

- 5 Chloroamide **5** (1.0 g, 2.5 mmol) was treated with dimethylamine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-11** (0.71 g, 67%) as a yellow solid.

- Mp > 320°C ¹H-NMR (DMSO) δ 2.19 (12H, s, N(CH₃)₂), 2.50 (4H, t, J 5.5 Hz, COCH₂CH₂N), 2.62 (4H, t, J 5.5 Hz, COCH₂CH₂N), 7.17 (2H, dd, J 1.9 Hz, J 8.8 Hz, H-2,7), 8.11 (2H, d, J 1.9 Hz, H-4,5) 8.17 (2H, d, J 8.8 Hz, H-1,8), 10.39 (2H, s, NHCO), 11.58 (1H, s, H-10), m/z (EI) 424.2346 (C₂₃H₃₀N₅O₃ M+H requires 424.2349), found C 62.41; H 7.02; N 15.75%, Calcd (anhydrous C₂₃H₂₉N₅O₃·1.0 mol H₂O) C 62.57; H 7.08; N 15.86%.

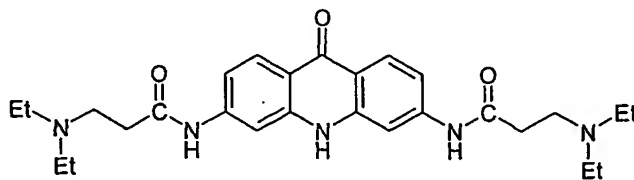
15

Example 11

Dihydrochloride Salt

(BR-ACO-6)

- 20 The dihydrochloride addition salt, **BR-ACO-6**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 123,6-Bis[3-(diethylamino)propionamido]-9(10*H*)-acridone**(BR-ACO-12)**

25

Chloroamide **5** (1.0 g, 2.5 mmol) was treated with diethylamine (3 mL) according to

- 82 -

the general aminolysis procedure to give the desired product **BR-ACO-12** (0.74 g, 62%) as a yellow solid.

Mp > 320°C; ¹H-NMR (CDCl₃) δ 1.70 (12H, t, J 7.2 Hz, N(CH₂CH₃)₂), 2.63 (4H, t, J 6.2 Hz, COCH₂CH₂N), 2.73 (8H, q, J 7.2 Hz, N(CH₂CH₃)₂), 2.83 (4H, t, J 6.2 Hz, COCH₂CH₂N), 6.76 (2H, dd, J 1.9 Hz, J 8.7 Hz, H-2,7), 8.36 (2H, d, J 1.9 Hz, H-4,5) 8.38 (2H, d, J 8.8 Hz, H-1,8), 9.63 (1H, s, H-10), 11.83 (2H, s, NHCO), m/z (EI) 480.2987 (C₂₇H₃₈N₅O₃ M+H requires 480.2375), found C 63.96; H 7.73; N 13.75%, Calcd (anhydrous C₂₇H₃₇N₅O₃·1.5 mol H₂O) C 64.01; H 7.96; N 13.82%.

Example 13

Dihydrochloride Salt

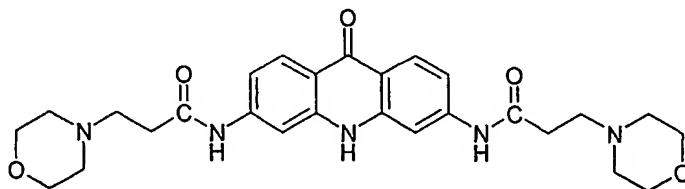
(**BR-ACO-7**)

The dihydrochloride addition salt, **BR-ACO-7**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 14

3,6-Bis[3-(morpholino)propionamido]-9(10*H*)-acridone

(**BR-ACO-13**)



Chloroamide **5** (1.0 g, 2.5 mmol) was treated with morpholine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-13** (1.10 g, 87%) as a pale yellow solid.

Mp > 320°C ¹H-NMR (DMSO) δ 2.43 (8H, t, J 4.5 Hz, N(CH₂CH₂)O), 2.55 (4H, t, J 6.8 Hz, COCH₂CH₂N), 2.67, 2.75 (4H, t, J 6.8 Hz, COCH₂CH₂N), 3.59 (8H, t, J 4.5 Hz, N(CH₂CH₂)O), 7.18 (2H, dd, J 1.8 Hz, J 8.8 Hz, H-2,7), 8.09 (2H, d, J 8.7 Hz, H-1,8), 8.11 (2H, d, J 1.8 Hz, H-4,5), 10.41 (2H, s, NHCO), 11.59 (1H, s, H-10),

- 83 -

m/z (EI) 508.22561 ($C_{27}H_{34}N_5O_5$ M+H requires 508.2560), found C 61.90; H 6.74; N 13.42%, Calcd (anhydrous $C_{27}H_{33}N_5O_5 \cdot 1.0$ mol H_2O) C 61.70; H 6.71; N 13.32%.

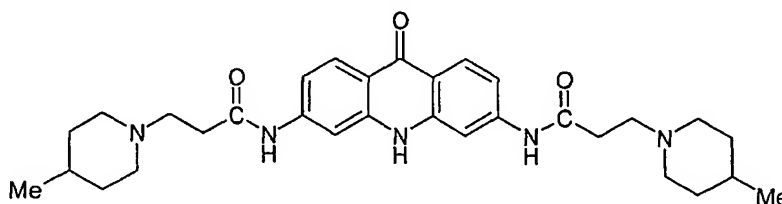
Example 15

Dihydrochloride Salt (BR-ACO-8)

The dihydrochloride addition salt, **BR-ACO-8**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 16

3,6-Bis[3-(4-methylpiperidino)propionamido]-9(10H)-acridone (BR-ACO-23)



Chloroamide **5** (1.0 g, 2.5 mmol) was treated with 4-methylpiperidine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-23** (0.75 g, 57%) as a pale yellow solid.

Mp > 320°C, 1H -NMR (DMSO) δ 0.90 (6H, d, J 6.3 Hz, 2 x CH_3), 1.19 (2H, m, $N(CH_2CH_2)_2CH$), 1.57 (4H, m, $N(CH_2CH_2)_2CH$), 1.95 (4H, m, NCH_2CH_2CH), 2.51 (8H, m, $N(CH_2CH_2)_2CH$), 2.56 (4H, t, J 7.1 Hz, $COCH_2CH_2N$), 2.85 (4H, t, J 7.1 Hz, $COCH_2CH_2N$), 7.16 (2H, dd, J 1.7 Hz, J 8.9 Hz, H-2,7), 8.09 (2H, d, J 8.9 Hz, H-1,8), 8.11 (2H, d, J 1.7 Hz, H-4,5), 10.51 (2H, s, $NHCO$), 11.60 (1H, s, H-10), m/z (EI) 532.3285 ($C_{31}H_{42}N_5O_3$ M+H requires 532.3288), found C 67.73; H 7.51; N 13.23%, Calcd (anhydrous $C_{31}H_{41}N_5O_3 \cdot 1.0$ mol H_2O) C 67.73; H 7.88; N 12.74%.

- 84 -

Example 17

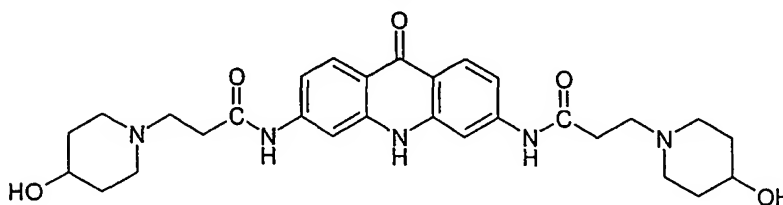
Dihydrochloride Salt

(BR-ACO-33)

- 5 The dihydrochloride addition salt, **BR-ACO-33**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 183,6-Bis[3-(4-hydroxypiperidino)propionamido]-9(10*H*)-acridone

(BR-ACO-24)



Chloroamide **5** (1.0 g, 2.5 mmol) was treated with 4-hydroxypiperidine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-24** (0.67 g, 50%) as a pale yellow solid.

15

Mp > 320°C, ¹H-NMR (DMSO) δ 1.44 (4H, m, N(CH₂CH_{2a})₂CH), 1.73 (4H, m, NCH₂CH_{2b})₂CH), 2.11 (4H, m, N(CH_{2a}CH₂)₂CH), 2.55 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.62 (4H, m, N(CH_{2b}CH₂)₂CH), 2.77 (4H, t, J 6.7 Hz, COCH₂CH₂N), 4.53 (2H, m, N(CH₂CH₂)₂CH), 7.16 (2H, dd, J 1.6 Hz, J 8.8 Hz, H-2,7), 8.07 (2H, d, J 8.8 Hz, H-1,8), 8.11 (2H, d, J 1.6 Hz, H-4,5), 10.52 (2H, s, NHCO), 11.61 (1H, s, H-10), m/z (EI) 536.2872 (C₂₉H₃₇N₅O₅ requires 536.2873), found C 61.77; H 7.00; N 13.39%, Calcd (anhydrous C₂₉H₃₇N₅O₅·1.5 mol H₂O) C 61.91; H 7.17; N 12.45%.

20

Example 19

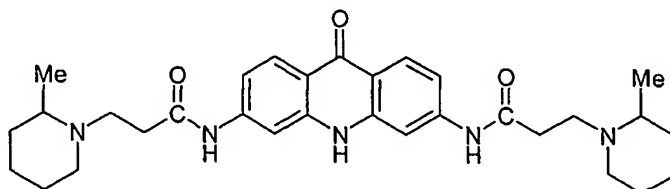
Dihydrochloride Salt

(BR-ACO-34)

25

The dihydrochloride addition salt, **BR-ACO-34**, of the compound in the previous example, was also prepared by treatment with HCl.

- 85 -

Example 203,6-Bis[3-(2-methylpiperidino)propionamido]-9(10*H*)-acridone (**BR-ACO-26**)

- 5 Chloroamide **5** (1.0 g, 2.5 mmol) was treated with 2-methylpiperidine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-26** (0.76 g, 57%) as a pale yellow solid.

Mp > 320°C, ¹H-NMR (DMSO) δ 1.19 (6H, d, J 6.3 Hz, CH₃), 1.62 (12H, m, CH₂),
10 2.34 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.56 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.68 (6H, m, NCH₂, NCH), 7.13 (2H, dd, J 1.6 Hz, J 8.8 Hz, H-2,7), 8.11 (2H, d, J 8.8 Hz, H-1,8), 8.14 (2H, d, J 1.6 Hz, H-4,5), 10.51 (2H, s, NHCO), 11.63 (1H, s, H-10), m/z (EI) 532.3286 (C₃₁H₄₁N₅O₃ M+H requires 532.3288), found C 67.66; H 7.38; N 12.61%, Calcd (anhydrous C₃₁H₄₁N₅O₃·1.0 mol H₂O) C 67.73; H 7.88; N 12.74%.

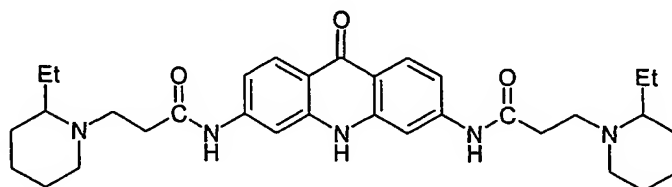
15

Example 21

Dihydrochloride Salt

(BR-ACO-36)

- 20 The dihydrochloride addition salt, **BR-ACO-36**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 223,6-Bis[3-(2-ethylpiperidino)propionamido]-9(10*H*)-acridone (**BR-ACO-27**)

25

Chloroamide **5** (1.0 g, 2.5 mmol) was treated with 2-ethylpiperidine (3 mL)

- 86 -

according to the general aminolysis procedure to give the desired product **BR-ACO-27** (0.79 g, 57%) as a pale yellow solid.

Mp > 320°C, ¹H-NMR (DMSO) δ 0.83 (6H, t, 7.1 Hz, CH₂CH₃), 1.39 (4H, m, CH₂CH₃), 1.52 (12H, m, CH₂), 2.24 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.51 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.71 (6H, m, NCH₂, NCH), 7.17 (2H, dd, J 1.6 Hz, J 8.8 Hz, H-2,7), 8.07 (2H, d, J 8.8 Hz, H-1,8), 8.11 (2H, d, J 1.6 Hz, H-4,5), 10.49 (2H, s, NHCO), 11.60 (1H, s, H-10), m/z (EI) 559.9994 (C₃₃H₄₅N₅O₃ requires 560.3601), found C 70.47; H 8.12; N 12.45%, Calcd (C₃₃H₄₅N₅O₃) C 70.81; H 8.1; N 12.51%.

Example 23

Dihydrochloride Salt

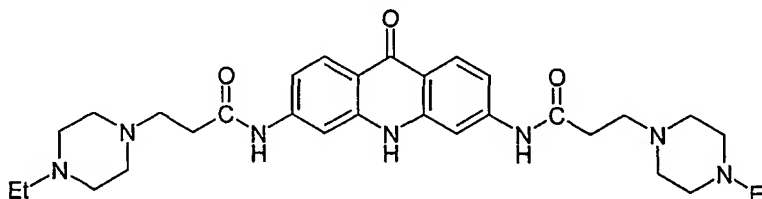
(**BR-ACO-37**)

- 15 The dihydrochloride addition salt, **BR-ACO-37**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 24

3,6-Bis[3-(N-ethylpiperazino)propionamido]-9(10*H*)-acridone

(**BR-ACO-29**)



Chloroamide **5** (1.0 g, 2.5 mmol) was treated with N-ethylpiperazine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-29** (0.76 g, 57%) as a pale yellow solid.

Mp > 320°C, ¹H-NMR (DMSO) δ 1.14 (6 H, t, CH₂CH₃), 1.62 (12H, m, CH₂), 2.34 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.56 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.65 (20H, m, NCH₂), 2.68 (6H, m, NCH₂, NCH), 7.13 (2H, dd, J 1.6 Hz, J 8.8 Hz, H-2,7), 8.11 (2H, d, J 8.8 Hz, H-1,8), 8.14 (2H, d, J 1.6 Hz, H-4,5), 10.51 (2H, s, NHCO),

- 87 -

11.63(1H, s, H-10), m/z (EI) 561.3427 ($C_{31}H_{42}N_7O_3$ M+H requires 561.3412), found C 67.66; H 7.38; N 12.61%, Calcd (anhydrous $C_{31}H_{41}N_5O_3 \cdot 1.0$ mol H_2O) C 63.94; H 7.72; N 16.82%.

5

Example 25

Dihydrochloride Salt

(BR-ACO-39)

The dihydrochloride addition salt, **BR-ACO-39**, of the compound in the previous example, was also prepared by treatment with HCl.

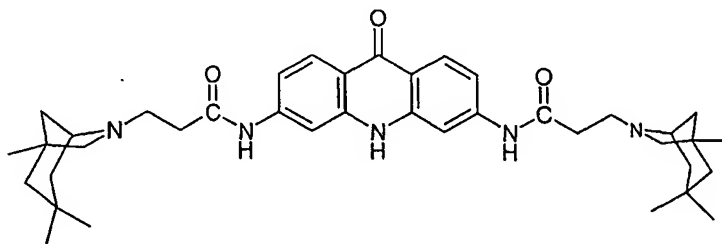
10

Example 26

3,6-Bis[(1,3,3-trimethyl-6-azabicyclo[3.2.1]-octanamino)propionamido]-9(10*H*)-acridone

15

(JH-ACO-31)



Chloroamide **5** (2.5 g, 5.9 mmol) was treated with 1,3,3-trimethyl-6-azabicyclo[3.2.1]-octane (7.0 mL) according to the general aminolysis procedure to give the desired product **JH-ACO-31** (3.1 g, 82%) as a yellow solid.

20

Mp > 320°C, 1H -NMR (DMSO) δ 0.84 (6H, s, CH_3), 1.02 (6H, s, CH_3), 1.25 (4H, m, CH_2) 1.07 (6H, s, CH_3), 1.21 (4H, m, CH_2), 1.34 (4H, m, CH_2), 2.34 (2H, m, CH), 2.63 (4H, t, $COCH_2$), 3.07 (4H, m, $COCH_2CH_2N$), 3.20–3.30 (4H, m, CH_2), 7.21 (2 H, d, J 8.8 Hz, H-1,8), 8.09 (2 H, s, H-4,5), 8.14 (2 H, d, J 8.8 Hz, H-2,7), 10.48 (2 H, s, $NHCO$), m/z (EI) 640.4238 ($C_{39}H_{53}N_5O_3$ M+H requires 640.4226).

25

- 88 -

Example 27

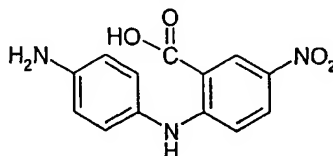
Dihydrochloride salt

(JH-ACO-32)

- 5 The dihydrochloride addition salt, **JH-ACO-32**, of the compound in the previous example, was also prepared by treatment with HCl.

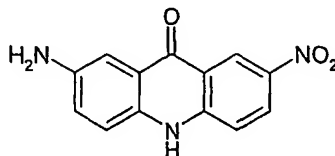
GROUP B: 2,7-ACRIDINES

10

Example 282-(4-Amino-phenylamino)-5-nitrobenzoic acid (**10**)

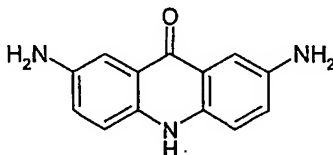
- A mixture of 2-chloro-5-nitrobenzoic acid **9** (150 g, 0.744 mol), 1,4-phenylenediamine **8** (150.0 g, 1.387 mol), anhydrous potassium carbonate (309 g, 2.236 mol), copper powder (2.0 g, 31.5 mol), cupric sulfate (10 mg) and water (2.25 l) was heated to reflux with stirring for 5 hr. It was then filtered hot through a fluted paper and allowed to stand overnight at room temperature. The potassium salt of the product was collected on a glass sinter and washed with ice-cold water (2 x 250 mL) followed by ice-cold ethanol (250 mL). The product was dissolved in boiling water (1250mL) and acetic acid was then added until there was no further precipitation. The mixture was cooled with an external ice water bath and the product collected. The product was washed with ice-cold water (3 x 500 mL) followed by ice-cold ethanol (2 x 500 mL), dry ether (250 mL) and finally hexane (2 x 500 mL). The product was dried over P₂O₅ under vacuum to yield a light brown solid **10** (130.52 g 64%).
- 15
- 20
- 25

- 89 -

Example 292-amino-7-nitro-9(10*H*)-acridone (**11**)

See Korolev et al., 1976. Polyphosphoric acid was freshly prepared by slowly
5 adding, with stirring, 85% orthophosphoric acid (360 mL) to phosphorus pentoxide
(600 g). The mixture was then heated on a steam bath with stirring until a clear
viscous liquid was obtained. 2-(4-amino-phenylamino)-5-nitrobenzoic acid **10**
(107.76 g, 0.394 mol) was added with stirring over the course of 5 min. Heating on
the steam bath was continued for 6 hr, the mixture being stirred occasionally.
10 Whilst still hot, the mixture was poured into 4 L of ice-water, stirred for 30 min, and
allowed to stand overnight. The mixture was adjusted to pH 8.0 by the addition of
0.88 s.g. aqueous ammonia, chilled for 2 hr, and the crude product collected on a
glass sinter. It was washed with dilute ammonia (1% 0.88 s.g. aqueous ammonia
in water, 250 mL) followed by water (3 x 250 mL), ice-cold ethanol (2 x 250 mL),
15 dry ether (2 x 250 mL) and finally hexane (250 mL). The product, **11**, was dried
over P₂O₅ under vacuum to yield a red-brown solid (97.04 g, 96%).

Mp > 350°C (lit. > 350°C; Korolev et al., 1976) ¹H-NMR (d₆-DMSO) δ 5.45 (2H, br s,
D₂O exchanges, -NH₂), 7.20 (1H, d, J 8.8 Hz, H-3), 7.38 (1H, s, H-1), 7.40 (1H, d, J
20 9.1 Hz, H-4), 7.58 (1H, d, 9.2 Hz, H-5), 8.35 (1H, d, 9.3 Hz, H-6), 8.98 (1H, s, H-8),
12.11 (1H, br s, D₂O exchanges, H-10).

Example 302,7-diamino-9(10*H*)-acridone (**12**)

25

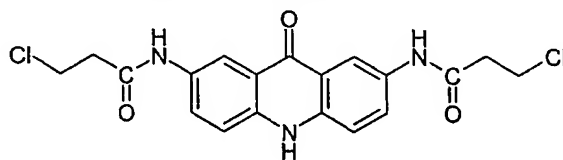
See Bogert et al., 1930. To a stirred suspension of 2-amino-7-nitro-9(10*H*)-
acridone **11** (22.5 g, 88.2 mmol) in ethanol was added, in one lot, a solution of

- 90 -

- sodium sulphide nonahydrate (94.5 g, 0.394 mol) and sodium hydroxide (37.5 g, 0.938 mol) in water (1.625 L). The mixture was refluxed with stirring for 16 hr. On cooling, saturated sodium bicarbonate solution (250 mL) was added and the total volume of the mixture reduced to 700 mL on a rotary evaporator. The flask was
- 5 chilled in ice for 3 hr after which the product was collected on a glass sinter. The product was washed with water (4 x 200 mL) followed by ice-cold ethanol (2 x 100 mL), dry ether (2 x 100 mL) and finally hexane (2 x 100 mL). The product, **12**, was dried over P₂O₅ under vacuum to yield an olive-green solid (18.70 g, 94%).
- 10 Mp 280°C dec. (lit. 325°C; Bogert et al. 1930) ¹H-NMR (d₆-DMSO) δ 4.98 (4H, br s, D₂O exchanges, -NH₂), 7.05 (2H, dd, J 2.5 Hz, J 8.8 Hz, H-3,6), 7.25 (2H, d, J 8.8 Hz, H-4,5), 7.31 (2H, d, J 2.4 Hz, H-1,8), 11.06 (1H, s, D₂O exchanges, H-10).

Example 31

- 15 2,7-Bis(3-chloropropionamido)-9(10H)-acridone (**13**)

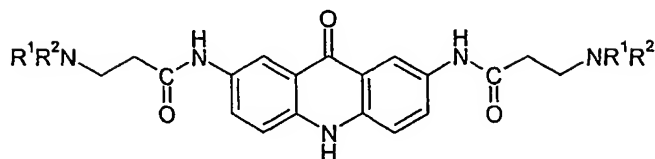


- A suspension of 2,7-diamino-9(10H)-acridone **12** (13.44 g, 60 mmol), in 3-chloropropionyl chloride (3-CPC) (240 mL) was stirred at 90°C for 4 hr and then heated under reflux for 2 hr. The resultant mixture was cooled to 0°C after which
- 20 the product was collected on a glass sinter. The product was washed with acetone (60 mL) followed by toluene (2 x 60 mL), more acetone (4 x 60 mL), dry ether (2 x 60 mL) and finally hexane (2 x 60 mL). The product was dried over P₂O₅ under vacuum to yield an olive-green solid (19.68 g, 81%).
- 25 Mp >350°C ¹H-NMR (d₆-DMSO) δ 2.86 (4H, t, J 6.5 Hz, COCH₂CH₂Cl), 4.01 (4H, t, J 6.5 Hz, COCH₂CH₂Cl), 7.63 (2H, d, J 8.7 Hz, H-4,5), 8.07 (2H, d, J 8.7 Hz, H-3,6), 8.61 (2H, s, H-1,8), 10.38 (2H, s, D₂O exchanges, NHCO), 11.86 (1H, s, D₂O exchanges, H-10).

- 91 -

Example 32

General Aminolysis Procedure (14)



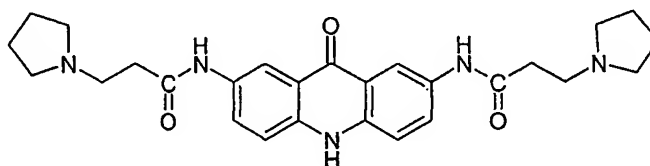
To a stirred refluxing suspension of **13** and NaI (0.3 g) in EtOH (70 mL) was added
 5 dropwise a suitable 2° amine, NHR^1R^2 (2.5 mL, 30 mmol) in EtOH (15 mL). The
 mixture was stirred at reflux for a further 3 hr. After cooling the majority of EtOH
 was removed under vacuum and then filtered, the collected solid was dissolved in
 CHCl_3 (100 mL) and washed with dilute ammonia solution (2 x 75 mL), brine
 (100 mL), dried and stirred over charcoal. The solvent was evaporated to produce
 10 a solid. Recrystallisation EtOH / DMF provided the desired amine **14**.

The acid addition salts of these amine derivatives, **15**, were prepared (by treatment
 with HCl) to increase solubility for biological evaluation.

15

Example 33

2,7-Bis[3-(pyrrolidino)propionamido]-9(10*H*)-acridone
 (BR-ACO-16)



Chloroamide **13** (400 mg, 1.0 mmol) was treated with pyrrolidine (3 mL) according
 20 to the general aminolysis procedure to give the desired product **BR-ACO-16**
 (348.mg, 74.4%) as a dark yellow solid.

Mp > 320°C, $^1\text{H-NMR}$ (DMSO) δ 1.69 (8H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.50 (8H, m,
 $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.52 (4H, t, J 7.2 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 2.74 (4H, t, J 7.2 Hz,
 25 $\text{COCH}_2\text{CH}_2\text{N}$), 7.49 (2H, d, J 9.0 Hz, H-4,5), 7.91 (2H, dd, J 2.4 Hz, J 9.0 Hz, H-
 3,6), 8.46 (2H, d, J 2.4 Hz, H-1,8), 10.20 (2H, s, NHCO), 11.702 (1H, s, H-10). m/z
 (EI) 476.2652 ($\text{C}_{27}\text{H}_{34}\text{N}_5\text{O}_3$ M+H requires 476.2662), found C, 66.43; H, 6.78; N,

- 92 -

14.72%, Calcd (anhydrous $C_{27}H_{33}N_5O_3 \cdot 0.7 \text{ mol H}_2O$) C, 66.43; H, 7.10; N, 14.35%.

Example 34

Dihydrochloride Salt

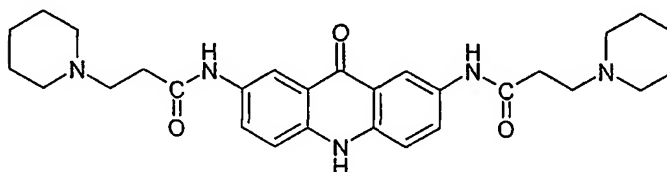
(BR-ACO-9)

The dihydrochloride addition salt, **BR-ACO-9**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 35

2,7-Bis[3-(piperidino)propionamido]-9(10*H*)-acridone

(BR-ACO-17)



Chloroamide **13** (400 mg, 1.0 mmol) was treated with piperidine (3 mL) according to the general aminolysis procedure to give the desired product **BR-ACO-17** (300mg, 61%) as a dark yellow solid.

Mp > 320°C, $^1\text{H-NMR}$ (CDCl_3) δ 1.56 (4H, m, $\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$), 1.67 (8H, m, $\text{N}(\text{CH}_2\text{CH}_2)\text{CH}_2$), 2.57 (8H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.65 (4H, t, J 6.7 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 2.79 (4H, t, J 6.7 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 7.65 (2H, d, J 8.8 Hz, H-4,5), 8.07 (2H, d, J 8.8 Hz, H-3,6) 8.61 (2H, s, H-1,8), 10.46 (1H, s, H-10) 11.85 (2H, s, NHCO) m/z (EI) 504.2973 ($\text{C}_{29}\text{H}_{38}\text{N}_5\text{O}_3$ M+H requires 504.2975), found C 64.47; H 7.56; N 12.83%, Calcd (anhydrous $\text{C}_{29}\text{H}_{37}\text{N}_5\text{O}_3 \cdot 2.0 \text{ mol H}_2\text{O}$) C 64.54; H 7.66; N 12.98%.

Example 36

Dihydrochloride Salt

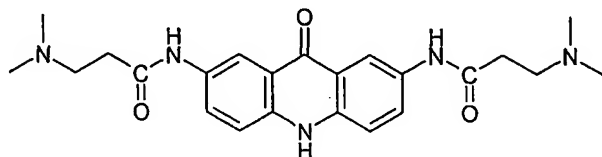
(BR-ACO-10)

The dihydrochloride addition salt, **BR-ACO-10**, of the compound in the previous example, was also prepared by treatment with HCl.

- 93 -

Example 37

2,7-Bis(3-dimethylaminopropionamido)-9(10*H*)-acridone
(JH-ACO-23)



5

Chloroamide **13** (1.0 g, 2.5 mmol) was treated with dimethylamine (7.0 mL) according to the general aminolysis procedure to give the desired product **JH-ACO-23** (630 mg, 61%) as a pale yellow solid.

- 10 Mp > 320°C. ¹H-NMR (DMSO) δ 2.25 (12H, s, N(CH₃)₂), 2.54 (4H, t, J 6.9 Hz, COCH₂CH₂N), 2.72 (4H, t, J 6.9 Hz, COCH₂CH₂N), 7.38 (2H, d, J 8.7 Hz, H-4,5), 7.89 (2H, dd, J 1.9 Hz, J 8.7 Hz, H-3,6), 8.51 (2H, d, J 1.9 Hz, H-1,8), 10.29 (2H, s, NHCO), 11.72 (1H, s, H-10), m/z (EI) 424.2346 (C₂₃H₃₀N₅O₃ M+H requires 424.2349), found C 63.51; H 7.04; N 16.20%, Calcd (anhydrous C₂₃H₂₉N₅O₃·0.7 mol H₂O) C 63.34; H 7.03; N 16.06%.
- 15

Example 38

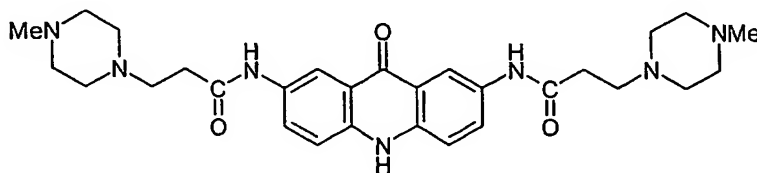
Dihydrochloride salt
(JH-ACO-22)

20

The dihydrochloride addition salt, **JH-ACO-22**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 39

2,7-Bis[3-(4'-N-methyl)piperizinopropionamido]-9(10*H*)-acridone
(JH-ACO-27)



25

- 94 -

Chloroamide **13** (1.0 g, 2.5 mmol) was treated with N-methylpiperazine (5 mL) according to the general aminolysis procedure to give the desired product **JH-ACO-27** (930 mg, 71%) as a pale yellow/green solid.

- 5 Mp > 320 °C. ¹H-NMR (DMSO) δ 2.34 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.56 (4H, t, J 6.7 Hz, COCH₂CH₂N), 2.65 (16H, m, NCH₂), 2.68 (6H, m, NCH₃), 7.38 (2H, d, J 8.6 Hz, H-4,5), 7.89 (2H, dd, J 1.9 Hz, J 8.6 Hz, H-3,6), 8.51 (2H, d, J 1.9 Hz, H-1,8), 10.29 (2H, s, NHCO), 11.72 (1H, s, H-10), m/z (EI) 533.3125 (C₂₉H₃₉N₇O₃ M+H requires 533.3114), found C 63.77; H 7.38, N 17.95%, Calcd (anhydrous C₂₉H₃₉N₇O₃ · 0.5 mol H₂O) C 64.18, H 7.43, N 18.07%.
- 10

Example 40

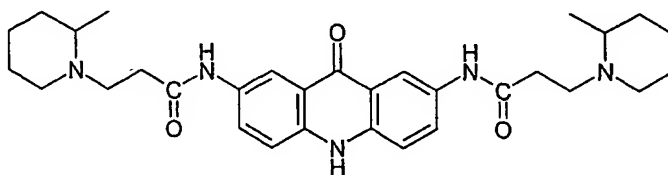
Dihydrochloride salt
(**JH-ACO-28**)

15

The dihydrochloride addition salt, **JH-ACO-28**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 41

- 20 2,7-Bis[3-(2-methylpiperidino)propionamido]-9(10H)-acridone
(**JM-ACO-06**)



- Chloroamide **13** (1.0 g, 2.5 mmol) was treated with 2-methylpiperidine (5 mL) according to the general aminolysis procedure to give the desired product
- 25 **JM-ACO-06** (916 mg, 69%) as a pale yellow/green solid.

¹H-NMR (DMSO) δ 1.21 (6 H, d, J 6.1 Hz, CH₃), 1.62 (12 H, m, CH₂), (8 H, m, N(CH₂CH₂)₂CH), 2.48 (4 H, t, 6.5 Hz, COCH₂CH₂N), 2.63 (6 H, m, NCH₂, NCH), 3.01 (4 H, m, COCH₂CH₂N), 7.58 (2H, d, J 8.9 Hz, H-4,5), 7.90 (2H, d, J 8.9 Hz, H-

- 95 -

3,6), 8.53 (2H, s, H 1,8), 9.48 (2H, s, NHCO), 10.57 (1H, s, H-10), m/z (EI) 532.3265 (C₃₁H₄₂N₅O₃ M+H requires 532.3288).

Example 42

5

Dihydrochloride salt

(JM-ACO-07)

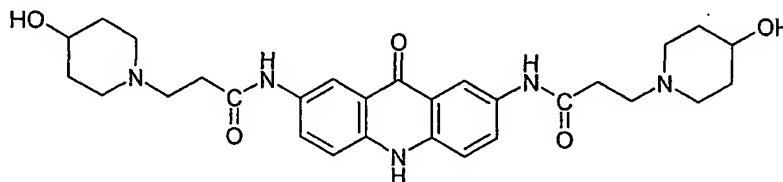
The dihydrochloride addition salt, **JM-ACO-07**, of the compound in the previous example, was also prepared by treatment with HCl.

10

Example 43

2,7-Bis[3-(4-hydroxypiperidino)propionamido]-9(10*H*)-acridone

(JM-ACO-08)



15 Chloroamide **13** (1.0 g, 2.5 mmol) was treated with 4-hydroxypiperidine (5 mL) according to the general aminolysis procedure to give the desired product **JM-ACO-08** (776 mg, 58%) as a pale yellow/green solid.

¹H-NMR (DMSO) δ 1.71 (8 H, m, N(CH₂CH₂)₂CH), 1.93 (8 H, m, N(CH₂CH₂)₂CH),
20 2.9 (12 H, m, CH₂) 3.01 (4 H, m, COCH₂CH₂N), 3.98(2 H, d, CH) 7.56 (2H, d, J 8.9 Hz, H-4,5), 7.91 (2H, d, J 8.9 Hz, H-3,6), 8.53 (2H, s, H 1,8), 10.02 (2H, s, NHCO), 11.47 (1H, s, H-10), m/z (EI) 558.2710 (C₂₉H₃₇N₅O₅ M+Na requires 558.2692), , found C 63.63; H 6.89, N 12.64%, Calcd (anhydrous C₂₉H₃₇N₅O₅.0.6 mol H₂O) C 63.74, H 7.05, N 12.82%.

25

Example 44

Dihydrochloride salt

(JM-ACO-09)

30 The dihydrochloride addition salt, **JM-ACO-09**, of the compound in the previous

- 96 -

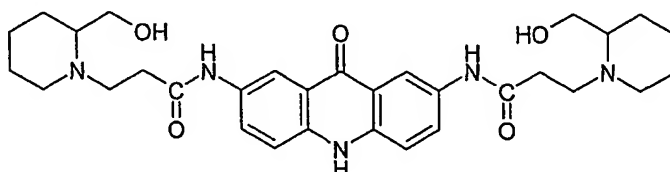
example, was also prepared by treatment with HCl.

Example 45

2,7-Bis[3-(2-hydroxymethylpiperidino)propionamido]-9(10*H*)-acridone

5

(**JM-ACO-11**)



Chloroamide **13** (1.0 g, 2.5 mmol) was treated with 2-hydroxymethylpiperidine (5 mL) according to the general aminolysis procedure to give the desired product **JM-ACO-11** (888 mg, 63%) as a pale yellow/green solid.

10

¹H-NMR (DMSO) δ 1.71 (4 H, m, CH₂), 1.77 (8 H, m, CH₂), 2.79 (2 H, m, CH), 2.9 (8 H, m, COCH₂CH₂N, NCH₂), 3.3 (4 H, m, COCH₂CH₂N), 3.6 (4 H, m, CH₂OH) 7.54 (2H, d, J 8.9 Hz, H-4,5), 7.91 (2H, d, J 8.9 Hz, H-3,6), 8.53 (2H, s, H 1,8), 9.48 (2H, s, NHCO), 10.57 (1H, s, H-10), m/z (EI) 564.3170 (C₃₁H₄₂N₅O₃ M+H requires 564.3186).

15

Example 46

Dihydrochloride salt

(**JM-ACO-12**)

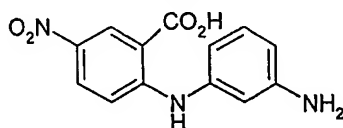
20

The dihydrochloride addition salt, **JM-ACO-12**, of the compound in the previous example, was also prepared by treatment with HCl.

- 97 -

GROUP C: 2,6-ACRIDONES**Example 47**

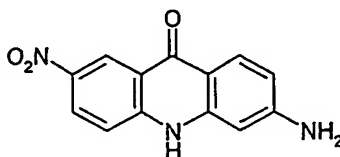
2-(3-Amino-phenylamino)-5-nitrobenzoic acid

(AR-ACO-06)

5 A mixture of 2-chloro-5-nitrobenzoic acid **16** (150.0 g, 744 mmol),
1,3-phenylenediamine **17** (150.0 g, 1.387 mol), anhydrous potassium carbonate
(309.0 g, 2.236 mol), copper powder (2.0 g, 31.5 mmol), cupric sulfate (10 mg)
10 and water (2.0 L) was heated to reflux with stirring for 6.25 hr under argon. It was
then allowed to stand overnight at room temperature. Glacial acetic acid was added
to the reaction mixture with stirring until pH 5 and the flask cooled in ice water. The
mustard yellow solid was collected, washed with ice-cold water (3 x 100 mL), and
redissolved in hot dilute ammonia (300 mL 0.88 s.g. ammonia and 2.7 L water).
15 Charcoal (2.0 g) was added, the mixture refluxed briefly, and then filtered through a
fluted paper. On cooling to room temperature the mixture was acidified to pH 5 by
adding glacial acetic acid and the flask cooled in ice-water. The product was
collected and washed with ice-cold water (2 x 100 mL) followed by ice-cold ethanol
(2 x 100 mL), dry ether (2 x 100 mL) and finally hexane (100 mL). The product was
20 dried over P₂O₅ under vacuum to yield the product **AR-ACO-06** (155.10 g, 76%) as
brown solid.

Mp 270 °C dec. (lit. 250 °C dec.; Goldstein and de Simo, 1927).

25

Example 483-Amino-7-nitro-9(10*H*)-acridone**(AR-ACO-07)**

- 98 -

2-(3-Amino-phenylamino)-5-nitrobenzoic acid (**AR-ACO-6**, 74 g, 270 mmol) was heated with concentrated sulphuric acid (500 mL) on a steam bath at 100°C for 105 min, chilled in ice-water, and then poured slowly onto crushed ice (2 kg). The mixture was allowed to stand at room temperature overnight before the product
5 was collected by filtration on a glass sinter and washed with distilled water (6 x 500 mL), followed by very dilute ammonia (2 x 500 mL, made by diluting 2 mL of 0.88 s.g. ammonia to 1 L), water (2 x 400 mL) and finally ethanol (200 mL). The product was dried at 105°C under vacuum for 4 hr to yield an olive-green solid **19** (60.50 g, 87.5%).

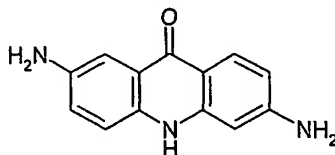
10

Mp 213 °C (lit. 216°C; Goldberg and Kelly 1946), ¹H-NMR (DMSO) δ 6.47 (1 H, d, J 1.9 Hz, H-4), 6.61 (1 H, dd, J 2.0 Hz & 8.8 Hz, H-2), 7.51 (1 H, d, J 9.2 Hz, H-5), 7.91 (1 H, d, J 8.8 Hz, H-1), 8.35 (1 H, dd, J 2.7 & 9.2 Hz, H-6), 8.88 (1 H, d, J 2.7 Hz, H-8), 11.78 (1 H, s, H-10).

15

Example 49

2,6-Diamino-9(10*H*)-acridone
(**AR-ACO-08**)



20 Finely ground 3-amino-7-nitro-9(10*H*)-acridone (**AR-ACO-7**, 22.50g, 88.1 mmol) was suspended in ethanol (950 mL) and stirred at reflux. A solution of sodium sulfide nonahydrate (94.75 g, 394 mmol) and sodium hydroxide (37.5 g, 938 mmol) in water (1.7 L) was added in one lot and refluxing continued for 20 hr. The mixture was allowed to cool to room temperature and ammonium bicarbonate (50 g) was
25 added in one lot and dissolved. The solution was reduced to about 500 mL on a rotary evaporator and allowed to stand overnight. The flask was chilled with ice-water, the product collected, and washed with ice cold water until the filtrate was a pale yellow-green colour. The crude product was dried then dissolved in boiling 1 M hydrochloric acid (900 mL). Charcoal (1 g) was added and the solution filtered
30 whilst hot through a fluted paper. The filtrate was basified to pH 8 by the addition of

- 99 -

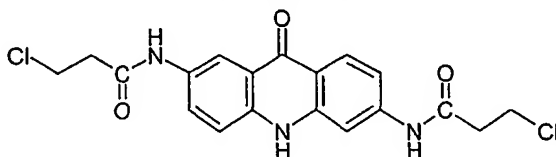
0.88 s.g. ammonia and the precipitate collected and was washed with water (2 x 20 mL) and dried over P_2O_5 under vacuum to yield a yellow solid **AR-ACO-08** (19.85 g, 61.2%).

- 5 Mp >350 °C (lit. 358-360°C; Goldberg and Kelly 1946); 1H -NMR (DMSO) δ 4.96 (2 H, s, 2-NH₂), 5.90 (2 H, s, 6-NH₂), 6.34 (1 H, s, H-5), 6.43 (1 H, d, J 8.7 Hz, H-7), 6.98 (1 H, dd, J 2.1 Hz & 7.5 Hz, H-3), 7.16 (1 H, d, J 8.7 Hz, H-4), 7.29 (1 H, s, H-1), 7.84 (1 H, d, J 8.7 Hz, H-8), 10.76 (1 H, s, H-10).

10

Example 50

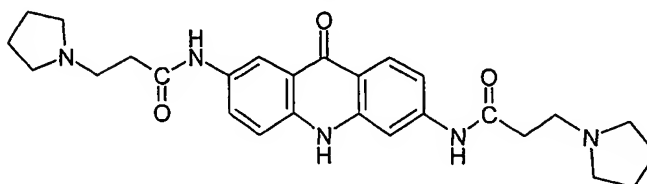
2,6-Bis (3-chloropropionamido)-9(10*H*)-acridone
(**AR-ACO-9**)



- 2,6-Diamino-9(10*H*)-acridone (**AR-ACO-8**, 8.40 g, 37.3 mmol) was suspended in 3-chloropropionyl chloride (100 mL), stirred at room temperature for 1 hr, at 90 °C for 15 1 hr, and at reflux for 6 hr. Allowed to stand at room temperature overnight and then chilled with ice-water. The product was collected and washed with acetone (2 x 30 mL) followed by toluene (3 x 30 mL), acetone again (4 x 30 mL), ethanol (2 x 30 mL), dry ether (2 x 30 mL) and finally hexane (2 x 30 mL). The product was 20 dried over P_2O_5 under vacuum to yield a yellow solid **AR-ACO-09** (12.96 g, 86%).

- Mp 335 °C dec., 1H -NMR (DMSO) δ 2.85 (2 H, t, J 6.2 Hz, 2-NHCOCH₂CH₂Cl), 2.92 (2 H, t, J 6.2 Hz, 6-NHCOCH₂CH₂Cl), 3.91 (2 H, t, J 6.1 Hz, 2-NHCOCH₂CH₂Cl), 3.92 (2 H, t, J 6.1 Hz, 6-NHCOCH₂CH₂Cl), 7.18 (1H, dd, J 1.8 25 Hz & 8.8 Hz, H-7), 7.48 (1 H, d, J 9.0 Hz, H-4), 7.93 (1 H, dd, J 2.4 Hz & 9.0 Hz, H-3), 8.14 (1 H, d, J 8.9 Hz, H-8), 8.20 (1 H, d, J 1.5 Hz, H-5), 8.45 (1 H, d, J 2.3 Hz, H-1), 10.23 (1 H, s, 2-NHCO), 10.47 (1 H, s, 6-NHCO), 11.71 (1 H, s, H-10).

- 100 -

Example 512,6-Bis [3-(pyrrolidino)propionamido]-9(10*H*)-acridone
(AR-ACO-10)

- 5 2,6-Bis (3-chloropropionamido)-9(10*H*)-acridone (**AR-ACO-9**, 3.00 g, 7.38 mmol) and KI (0.10 g, 0.60 mmol) were suspended in a mixture of dimethylformamide (45 mL) and ethanol (45 mL). Pyrrolidine (12 mL, 10.22 g, 144 mmol) was added in one lot and the whole stirred at reflux for 21 hr. The flask was cooled and all the solvents removed under reduced pressure. Dimethylformamide (100 mL) was
- 10 added to the flask and this was in turn removed under reduced pressure. The process was repeated with toluene (2 x 100 mL) and propan-2-ol (2 x 100 mL). The solid in the flask was dissolved in water (60 mL) and 0.88 s.g. ammonia (10 mL) was added dropwise with stirring to yield an orange-brown precipitate. The flask was chilled with ice-water and the product collected, washed with dilute ammonia
- 15 (2 x 10 mL, 1% dilution of 0.88 s.g. ammonia) and ice-cold water (2 x 10 mL). The product was dried in air and over P₂O₅ under vacuum to yield a yellow solid **AR-ACO-10** (3.11 g, 87%).

- Mp 299 °C dec., ¹H-NMR (DMSO) δ 1.76 (8 H, m, N(CH₂CH₂)₂), 2.51 (8 H, m, N(CH₂CH₂)₂), 2.56 (4 H, t, J 6.8 Hz, COCH₂CH₂N), 2.74 (2 H, t, J 7.0 Hz, 2-NHCOCH₂CH₂N), 2.76 (2 H, t, J 7.0 Hz, 6-NHCOCH₂CH₂N), 7.13 (1 H, dd, J 1.7 Hz & 8.9 Hz, H-7), 7.46 (1 H, d, J 8.9 Hz, H-4), 7.92 (1 H, dd, J 2.2 Hz & 9.0 Hz, H-3), 8.12 (1 H, d, J 8.8 Hz, H-8), 8.21 (1 H, d, J 1.7 Hz, H-5), 8.43 (1 H, d, J 2.2 Hz, H-1), 10.19 (1 H, s, 2-NHCO), 10.50 (1H, s, 6-NHCO), 11.67 (1 H, s, H-10).

- 101 -

Example 52

Dihydrochloride salt

(AR-ACO-11)

- 5 The dihydrochloride addition salt, **AR-ACO-11**, of the compound in the previous example, was also prepared by treatment with HCl.

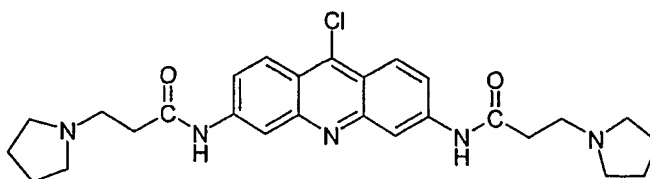
GROUP D: 3,6,9-ACRIDINES

10

Example 53

2,7-Bis[3-(pyrrolidino)propionamido]-9-chloroacridine

(BR-ACO-18)



A suspension of **BR-ACO-14** (5 g, 10 mmol) in POCl₃ (75 mL) was refluxed for 2 hr.

- 15 After cooling to 0°C the suspension was filtered and the collected solid washed with toluene (2 x 50 mL) and Et₂O (2 x 100 mL). The product was collected and redissolved in CHCl₃ (100 mL) and washed with dilute ammonia solution (2 x 75 mL), brine (100 mL), dried and treated with charcoal. Evaporation under reduced pressure provided the product, **BR-ACO-18**, as a green brown solid.

20

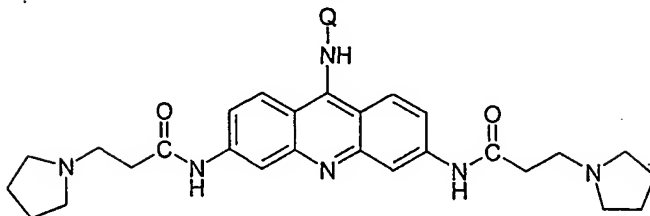
¹H-NMR (CDCl₃) δ 1.97 (8H, m, N(CH₂CH₂)₂), 2.62 (4H, t, J 6.3 Hz, COCH₂CH₂N), 2.75 (8H, m, N(CH₂CH₂)₂), 2.92 (4H, t, J 6.3 Hz, COCH₂CH₂N), 7.97 (2H, dd, J 2.1 Hz J 9.4 Hz, H-2,7), 8.10 (2H, d, J 2.1 Hz, H-4,5), 8.33 (2H, d, J 9.4 Hz, H-1,8), 11.82 (2H, s, NHCO). *m/z* (EI) 494.2342 (required C₂₇H₃₃N₅O₂Cl M+H 494.2323)

- 25 Found: C, 64.76; H, 6.45; N, 13.93%. C₂₇H₃₂N₅O₂Cl.0.4 H₂O requires C, 64.70; H, 6.601; N, 13.97%.

- 102 -

Example 54

9-Substitution General Procedure

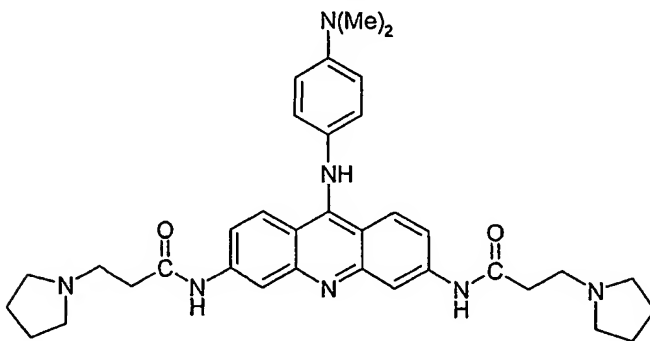


To a vigorously stirred solution of **BR-ACO-18** in CHCl_3 was added dropwise a
 5 solution of the proposed amine, Q-NH_2 (e.g., $\text{NH}_2(\text{CH}_2)_p\text{NH}_2$, substituted anilines),
 for example, in CHCl_3 . This solution was stirred for a further 2 hr, the solvent was
 then removed under reduced pressure and the resultant solid washed with EtOH
 and Et₂O to give the desired trisubstituted derivative.

10

Example 55

N-{9-[4'-(N,N-Dimethylamino)phenylamino]}-3,6-
 bis(3-pyrrolidinopropionamido)acridine
 (**BR-ACO-21**)



15 3,6-Bisamido-9-chloroacridone **BR-ACO-18** (400 mg, 0.8 mmol) was treated with
 4-N,N-dimethylaminoaniline (0.5 mL) according to the general procedure to give the
 desired product **BR-ACO-21** (400 mg, 88%) as a brown solid.

Mp > 320°C, ¹H-NMR (DMSO) δ 1.81 (8 H, m, N(CH₂CH₂)₂), 2.81 (4H, t, J 6.9 Hz,
 20 COCH₂CH₂N), 2.85 (8H, m, N(CH₂CH₂)₂), 3.16 (4H, t, J 6.9 Hz, COCH₂CH₂N), 6.67
 (2H, d, J 8.7 Hz, H-2,7), 6.96 (2H, d, J 8.7 Hz, H-1,8), 7.26 (2H, d, J 8.6 Hz, H-
 3',5'), 8.03 (2H, d, J 8.6 Hz, H-2',6'), 8.34 (2H, s, H-4,5), 10.92 (2H, s, NHCO), m/z

- 103 -

(EI) 594.3540 (requires $C_{35}H_{40}N_7O_2$ M+H 594.3556).

Example 56

Trihydrochloride Salt

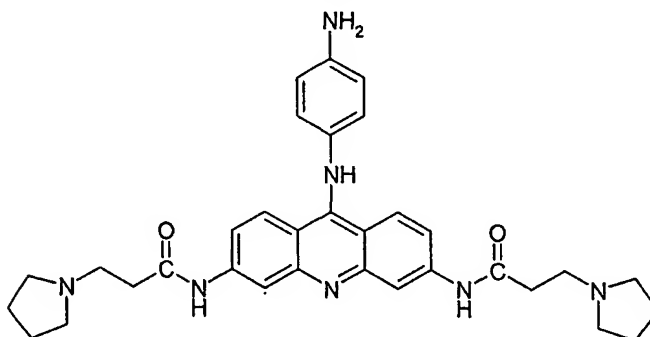
(BR-ACO-19)

The trihydrochloride addition salt, **BR-ACO-19**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 57

N-[9-(4'-Aminophenylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine

(BR-ACO-22)



3,6-bisamido-9-chloroacridone **BR-ACO-18** (400 mg, 0.8 mmol) was treated with 1,4-phenylenediamine (0.5 mL) according to the general procedure to give the desired product **BR-ACO-22** (400 mg, 88%) as a brown solid.

Mp > 320°C, $^1\text{H-NMR}$ (DMSO) δ 1.81 (8 H, m, $N(\text{CH}_2\text{CH}_2)_2$), 2.74 (4H, t, J 6.7 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 2.85 (8H, m, $N(\text{CH}_2\text{CH}_2)_2$), 2.93 (6H, s, $N(\text{CH}_3)_2$), 3.07 (4H, t, J 6.7 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 6.78 (2H, d, J 8.9 Hz, H-2,7), 6.99 (2H, d, J 8.9 Hz, H-1,8), 7.20 (2H, d, J 9.1 Hz, H-3',5'), 7.97 (2H, d, J 9.1 Hz, H-2',6'), 8.24 (2H, s, H-4,5), 10.81 (2H, s, NHCO), m/z (EI) 566.3260 (requires $C_{33}H_{44}N_7O_2$ M+H 566.3243).

- 104 -

Example 58

Trihydrochloride Salt

(BR-ACO-20)

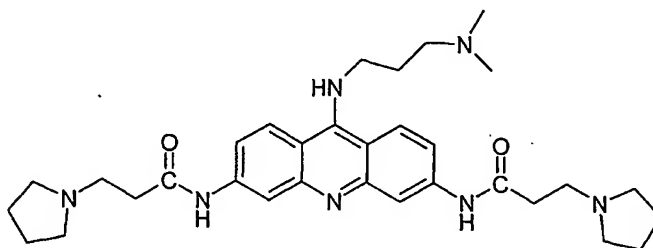
- 5 The trihydrochloride addition salt, **BR-ACO-20**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 59

N-{9-[3-(*N,N*-Dimethyl)aminopropylamino]}-3,6-
bis(3-pyrrolidinopropionamido)acridine

10

(JH-ACI-64)



- 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with
15 *N,N*-dimethylpropylenediamine (0.4 mL) according to the general procedure to give the desired product **JH-ACI-64** (390 mg, 70%) as a pale brown solid.

- ¹H-NMR (CDCl₃) δ 1.86 (10 H, m, N(CH₂CH₂)₂, HNCH₂CH₂CH₂NMe₂), 2.29 (6 H, s, N(CH₃)₂), 2.49-2.55 (6 H, m, COCH₂CH₂N, HNCH₂CH₂CH₂NMe₂), 2.63 (8 H, m, N(CH₂CH₂)₂), 2.79-2.83 (4 H, m, COCH₂CH₂N), 3.74-3.78 (2 H, t, J 5.6 Hz, HNCH₂CH₂CH₂NMe₂), 7.61-7.62 (2 H, d, J 1.9 Hz, H-4,5), 7.84-7.88 (2 H, dd, J 9.3 and 1.9 Hz, H-2,7), 8.00-8.03 (2 H, d, J 9.3 Hz, H-1,8), 11.49 (2 H, s, NHCO), *m/z* (EI) 560.3730 (C₃₂H₄₆N₇O₂ M+H requires 560.3713).
- 20

- 105 -

Example 60

Tetrahydrochloride Salt

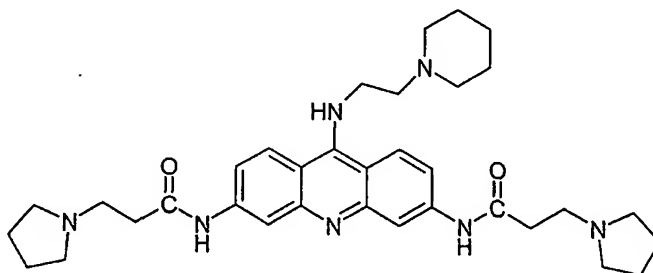
(JH-ACI-65)

- 5 The tetrahydrochloride addition salt, **JH-ACI-65**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 61*N*-[9-(2-Piperidin-1-yl-ethylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine

10

(JH-ACI-68)



3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 1-(2-aminoethyl)piperidine (0.4 mL) according to the general procedure to give the desired product **JH-ACI-68** (210 mg, 36%) as an orange solid.

15

- ¹H-NMR (CDCl₃) δ 1.54-1.56 (2 H, m, N(CH₂CH₂)₂CH₂), 1.68-1.72 (4 H, m, N(CH₂CH₂)₂CH₂), 1.94-1.96 (8 H, m, N(CH₂CH₂)₂), 2.43-2.44 (4 H, m, N(CH₂CH₂)₂CH₂), 2.59-2.68 (6 H, m, COCH₂CH₂N and HNCH₂CH₂N), 2.73 (8 H, m, N(CH₂CH₂)₂), 2.88-2.93 (4 H, m, COCH₂CH₂N), 3.85-3.89 (2 H, m, HNCH₂CH₂N), 6.76 (1 H, s, NH), 7.67 (2 H, d, J 2.0 Hz, H-4,5), 7.98-8.02 (2 H, dd, J 9.4 and 2.0 Hz, H-2,7), 8.12-8.16 (2 H, d, J 9.4 Hz, H-1,8), 11.58 (2 H, s, NHCO), *m/z* (EI) 586.3845 (C₃₄H₄₈N₇O₂ M+H requires 586.3869).
- 20

Example 62

25

Tetrahydrochloride Salt

(JH-ACI-69)

The tetrahydrochloride addition salt, **JH-ACI-69**, of the compound in the previous

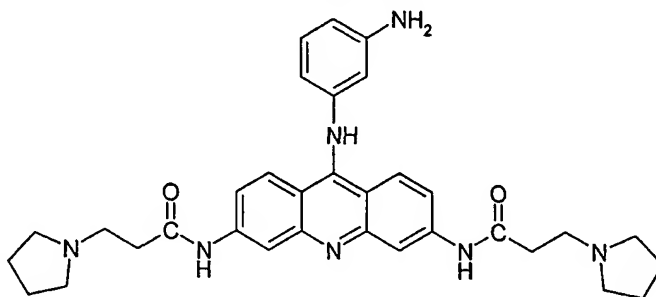
- 106 -

example, was also prepared by treatment with HCl.

Example 63

N-(9-[3'-(Amino)phenylamino])-3,6-bis(3-pyrrolidinopropionamido)acridine

(JH-ACI-73)



3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 1,3-phenylenediamine (0.5 mL) according to the general procedure to give the desired product **JH-ACI-73** (446 mg, 78%) as an orange solid.

Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.94 (8 H, m, N(CH₂CH₂)₂), 2.62 (4 H, t, J 6.5 Hz, COCH₂CH₂N), 2.72 (8 H, m, N(CH₂CH₂)₂), 2.89 (4 H, t, J 6.5 Hz, COCH₂CH₂N), 3.62 (2 H, sbr, NH₂), 6.12 (1 H, m, H-5'), 6.21 (1 H, s, H-2'), 6.34 (2 H, m, H-4',6'), 6.96 (2 H, m, H-4,5), 7.99 (4 H, m, H-1,2,7,8), m/z (EI) 566.3219 (C₃₃H₄₀N₇O₂ M+H requires 566.3243), found C 67.07; H 7.06, N 16.59%, Calcd (anhydrous C₃₃H₃₉N₇O₂·1.2 mol H₂O) C 67.48, H 7.10, N 16.69%.

Example 64

Trihydrochloride Salt

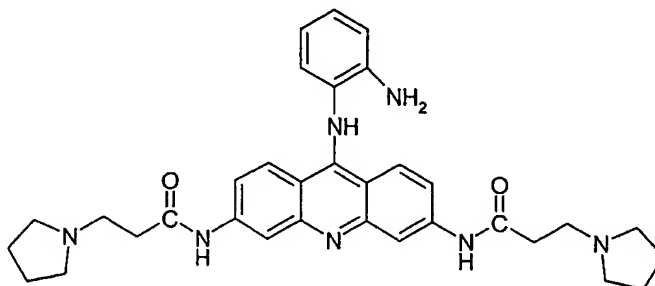
(JH-ACI-74)

The trihydrochloride addition salt, **JH-ACI-74**, of the compound in the previous example, was also prepared by treatment with HCl.

- 107 -

Example 65

N-[9-(2'-(Amino)phenylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JH-ACI-75**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 1,2-phenylenediamine (0.5 mL) according to the general procedure to give the desired product **JH-ACI-76** (400 mg, 88%) as an orange solid.

- 10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.90 (8 H, m, N(CH₂CH₂)₂), 2.4 (8 H, m, N(CH₂CH₂)₂), 2.55 (4 H, m, COCH₂CH₂N), 2.68 (4 H, m, COCH₂CH₂N), 3.49 (2 H, sbr, NH₂), 6.80 (6 H, m, 4Ar-H, H-1,8), 7.95 (4 H, m, H-2,4,5,7), m/z (EI) 566.3219 (C₃₃H₄₀N₇O₂ M+H requires 566.3243), found C 66.67; H 7.09, N 16.49%, Calcd (anhydrous C₃₃H₃₉N₇O₂·1.4 mol H₂O) C 67.07, H 7.13, N 16.59%.

15

Example 66

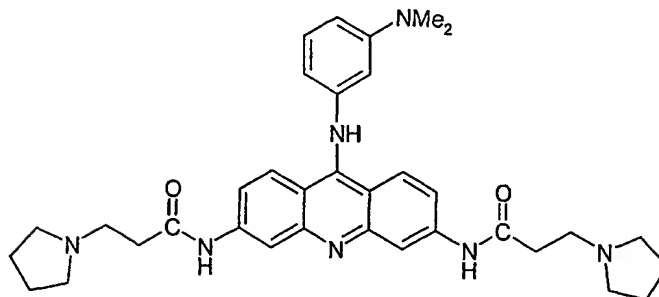
Trihydrochloride Salt
(**JH-ACI-76**)

- 20 The trihydrochloride addition salt, **JH-ACI-76**, of the compound in the previous example, was also prepared by treatment with HCl.

- 108 -

Example 67

N-{9-[3'-(*N,N*-Dimethylamino)phenylamino]}-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JH-ACI-77**)



5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with *N,N*-dimethyl-1,3-phenylenediamine (0.5 mL, freshly prepared from the hydrochloride salt) according to the general procedure to give the desired product **JH-ACI-77** (400 mg, 88%) as a brown solid.

10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.91 (8 H, m, N(CH₂CH₂)₂), 2.60 (4 H, m, COCH₂CH₂N), 2.67 (8 H, m, N(CH₂CH₂)₂), 2.88 (6 H, s, N(CH₃)₂), 2.90 (4 H, m, COCH₂CH₂N), 6.14 (1 H, d, J 7.9 Hz, H-4'), 6.30 (1 H, s, H-2'), 6.39 (1 H, d, J 8.1 Hz, H-6'), 7.11 (1 H, dd, J 7.9 Hz 8.1 Hz, H-5'), 7.9 (6 H, m, H-1,2,4,5,7,8), 11.58 (2

15 H, s, NHCO), m/z (EI) 594.3572 (C₃₅H₄₃N₇O₂ M+H requires 594.3556), found C 66.62; H 6.9, N 15.54%, Calcd (anhydrous C₃₅H₄₂N₇O₂ · 2.0 mol H₂O) C 66.86, H 7.37, N 15.59%.

Example 68

20 Trihydrochloride Salt
(**JH-ACI-78**)

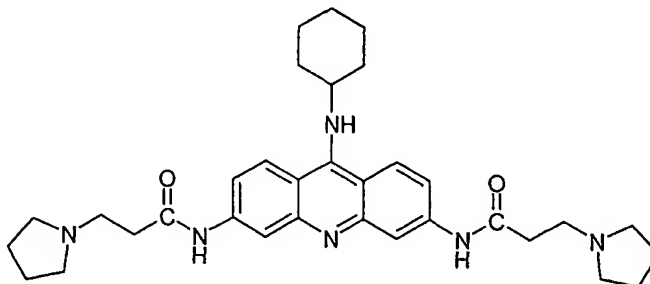
The trihydrochloride addition salt, **JH-ACI-78**, of the compound in the previous example, was also prepared by treatment with HCl

25

- 109 -

Example 69

N-[9-(Cyclohexylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JH-ACI-81**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with cyclohexylamine (0.5 mL) according to the general procedure to give the desired product **JH-ACI-81** (484 mg, 86%) as yellow solid.

- 10 Mp >300 °C, ¹H-NMR (CDCl₃) δ 1.23 (14 H, m, CH₂), 1.68 (2 H, m, CH₂), 1.76 (4 H, m, CH₂), 1.92 (2 H, m, CH₂), 2.12 (4 H, m, CH₂), 2.5 (4 H, m, CH₂), 2.88 (4 H, m, CH₂), 3.06 (1 H, m, CH), 3.83 (1 H, sbr, NH), 7.78 (2 H, d, J 8.8 Hz, H-2,7), 7.96 (2 H, s, H-4,5), 7.97 (2 H, d, J 8.8 Hz, H-1,8), 11.38 (2 H, sbr, NHCO), m/z (EI) 556.3534 (C₃₃H₄₅N₆O₂ M+H requires 556.3526), found C 68.60; H 7.97, N 14.54%, Calcd (anhydrous C₃₃H₄₄N₆O₂·1.2 mol H₂O) C 67.48, H 8.09, N 14.53%.

15

Example 70

Trihydrochloride Salt

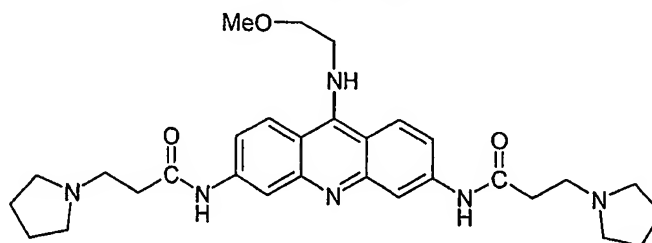
(JH-ACI-82)

- 20 The trihydrochloride addition salt, **JH-ACI-82**, of the compound in the previous example, was also prepared by treatment with HCl.

- 110 -

Example 71

N-[9-(2-Methoxy-ethylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JH-ACI-85**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 2-methoxyethylamine (0.5 mL) according to the general procedure to give the desired product **JH-ACI-85** (290 mg, 54%) as a brown solid.

- Mp <100 °C, ¹H-NMR (DMSO) δ 1.88 (8 H, m, N(CH₂CH₂)₂), 2.65 (6 H, m, COCH₂CH₂N and HNCH₂CH₂OMe), 2.68 (8 H, m, N(CH₂CH₂)₂), 2.87-2.92 (4 H, m, COCH₂CH₂N), 4.7.2 (5 H, m, HNCH₂CH₂OCH₃), 7.59 (2 H, d, J 1.9 Hz, H-4,5), 7.94-7.99 (2 H, dd, J 9.4 and 1.9 Hz, H-2,7), 8.05-8.08 (2 H, d, J 9.4 Hz, H-1,8), 11.54 (2 H, s, NHCO), m/z (EI) 533.3231 (C₃₀H₄₁N₆O₃ M+H requires 533.3240).
- 10

15

Example 72

Trihydrochloride Salt

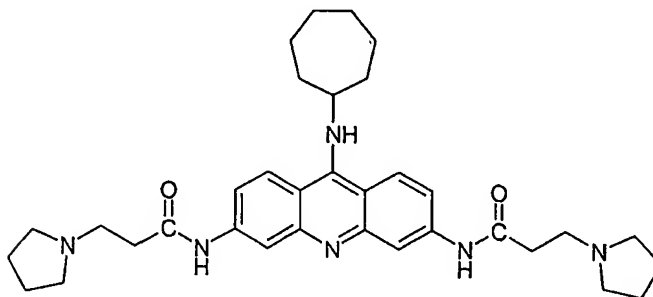
(JH-ACI-86)

- The trihydrochloride addition salt, **JH-ACI-86**, of the compound in the previous
20 example, was also prepared by treatment with HCl.

- 111 -

Example 73

N-[9-(Cycloheptylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JH-ACI-87**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with cycloheptylamine (0.5 mL) according to the general procedure to give the desired product **JH-ACI-87** (485 mg, 84%) as a yellow solid.

Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.62 (16 H, m, CH₂), 2.1 (4 H, m, CH₂), 2.43 (4 H, m, CH₂), 2.55 (4 H, m, J 5.0 Hz, CH₂), 2.70 (4 H, m, J 5.0 Hz, CH₂), 2.92 (1 H, t, J 5.1 Hz, CH), 4.08 (1 H, sbr, NH), 7.92 (2 H, m, H-2,7), 8.33 (4 H, m, H-1,4,5,8), m/z (EI) 571.3735 (C₃₄H₄₇N₆O₂ M+H requires 571.3761).

10

Example 74

15 Trihydrochloride Salt
(**JH-ACI-88**)

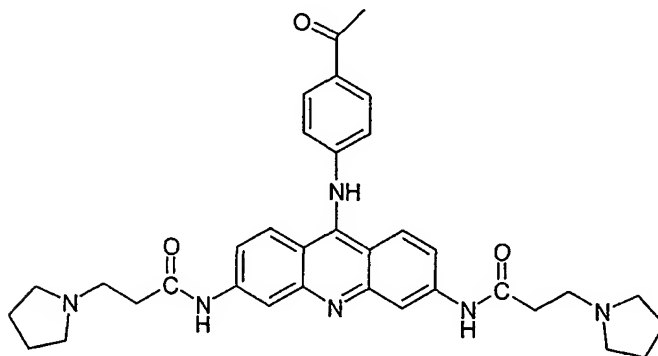
The trihydrochloride addition salt, **JH-ACI-88**, of the compound in the previous example, was also prepared by treatment with HCl.

20

- 112 -

Example 75

N-[9-(4'-Acetylphenylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JH-ACI-89**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 4-aminoacetophenone (0.5 mL) according to the general procedure to give the desired product **JH-ACI-89** (400 mg, 88%) as an orange solid;
- 10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.69 (8 H, m, N(CH₂CH₂)₂), 2.18 (7 H, m, COCH₂CH₂N, COCH₃), 2.51 (8 H, m, N(CH₂CH₂)₂), 2.76 (4 H, m, COCH₂CH₂N), 6.81 (2 H, d, J 7.9 Hz, 2-ArH), 6.90 (2 H, d, J 7.9 Hz, 2-ArH), 7.88 (2 H, d, H-2,7), 8.10 (4 H, m, H-1,4,5,8), 10.36 (2 H, sbr, NHCO), m/z (EI) 566.3219 (C₃₃H₄₀N₇O₂ M+H requires 566.3243), found C 67.07; H 7.06, N 16.59%, Calcd (anhydrous C₃₃H₃₉N₇O₂·1.2 mol H₂O) C 67.48, H 7.10, N 16.69%.

15

Example 76

Trihydrochloride Salt

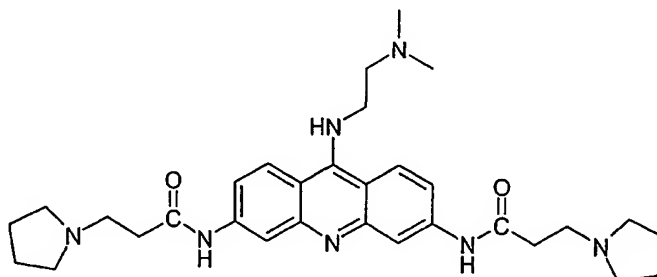
(JH-ACI-90)

- 20 The trihydrochloride addition salt, **JH-ACI-90**, of the compound in the previous example, was also prepared by treatment with HCl.

- 113 -

Example 77

N-[9-(*N,N*-Dimethylethylenediamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/152**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with *N,N*-dimethylethylenediamine (0.03 mL) according to the general procedure to give the desired product **BSU-SB-36/152** (370 mg, 67%) as a yellow solid.

- ¹H-NMR (CDCl₃) δ 1.88-1.95 (8 H, m, N(CH₂CH₂)₂), 2.42 (6 H, s, N(CH₃)₂), 2.58-2.68 (6 H, m, COCH₂CH₂N and HNCH₂CH₂NMe₂), 2.72 (8 H, m, N(CH₂CH₂)₂), 2.87-2.92 (4 H, m, COCH₂CH₂N), 4.06-4.10 (2 H, t, J 5.6 Hz, HNCH₂CH₂NMe₂), 7.59 (2 H, d, J 1.9 Hz, H-4,5), 7.94-7.99 (2 H, dd, J 9.4 and 1.9 Hz, H-2,7), 8.05-8.08 (2 H, d, J 9.4 Hz, H-1,8), 11.54 (2 H, s, NHCO), *m/z* (EI) 546.3570 (C₃₁H₄₄N₇O₂ M+H requires 546.3556).

15

Example 78

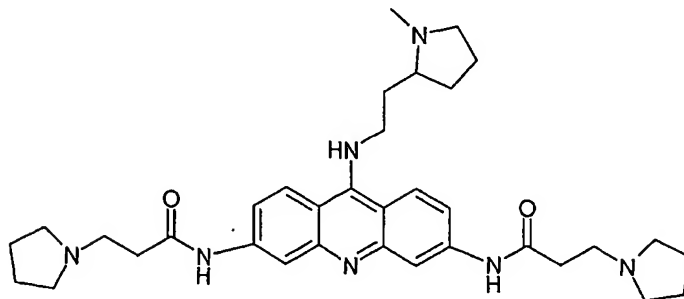
Tetrahydrochloride Salt
(**SB-ACI-11**)

- 20 The tetrahydrochloride addition salt, **SB-ACI-11**, of the compound in the previous example, was also prepared by treatment with HCl.

- 114 -

Example 79

N-{9-[2-(2'-Aminoethyl)-1-methylpyrrolidino]}-3,6-bis(3-pyrrolidinopropionamido)acridine
(BSU-SB-36/158)



5

3,6-Bisamido-9-chloroacridine **BR-ACO-18** (0.5 mg, 1.0 mmol) was treated with 2-(2-aminoethyl)-1-methylpyrrolidine (0.43 mL) according to the general procedure to give the desired product **BSU-SB-36/158** (380 mg, 64%) as a yellow solid.

- 10 $^1\text{H-NMR}$ (CDCl_3) δ 1.76-1.89 (4 H, m, $\text{MeN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}-)$, 1.96 (10 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$ and $\text{HNCH}_2\text{CH}_2-$), 2.08-2.28 (2 H, m, $\text{MeN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}-)$, 2.51 (3 H, s, NCH_3), 2.58-2.63 (4 H, t, J 5.3 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 2.72, (8 H, m, $\text{COCH}_2\text{CH}_2\text{N}$), 2.88-2.92 (4 H, m, t, J 5.3 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 3.23-3.29 (1 H, m, $\text{MeN}(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}-)$, 4.09-4.20 (2 H, m, $\text{HNCH}_2\text{CH}_2-$), 7.58-7.59 (2 H, d, J 2.0 Hz, H-4,5), 7.96-8.02 (2 H, m, H-2,7), 8.05-8.09 (2 H, m, J 9.4 Hz, H-1,8), 8.39 (1 H, s, NH), 11.55 (2 H, s, NHCO), m/z (EI) 586.3840, ($\text{C}_{34}\text{H}_{48}\text{N}_7\text{O}_2$ M^+H requires 586.3869).
- 15

Example 80

20

Tetrahydrochloride Salt
(SB-ACI-12)

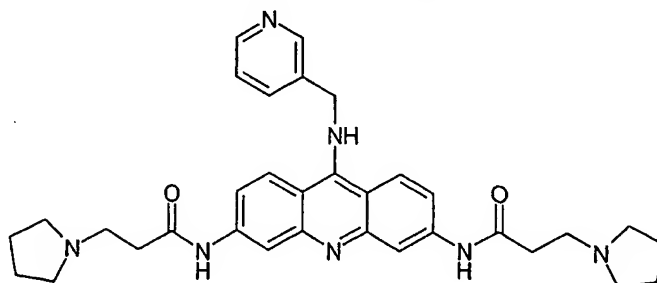
The tetrahydrochloride addition salt, **SB-ACI-12**, of the compound in the previous example, was also prepared by treatment with HCl.

25

- 115 -

Example 81

N-[9-(Pyridin-3'-yl-methylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/160**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with pyridin-3-yl-methylamine (0.31 mL) according to the general procedure to give the desired product **BSU-SB-36/160** (220 mg, 39%) as a yellow solid.

- ¹H-NMR (CDCl₃) δ 1.85 (8 H, m, N(CH₂CH₂)₂), 2.48-2.53 (4 H, dd, J 5.3 and 6.0 Hz, COCH₂CH₂N), 2.63 (8 H, m, N(CH₂CH₂)₂), 2.78-2.83 (4 H, dd, J 5.3 and 6.0 Hz, COCH₂CH₂N), 4.91 (2 H, s, HNCH₂Aryl), 7.18-7.23 (1 H, m, H-5'), 7.62-7.65 (2 H, m, H-2, 7), 7.76 (2 H, m, H-4, 5), 7.91-7.95 (2 H, d, J 9.2 Hz, H-1,8), 8.49-8.50 (2 H, m, H-4', 6'), 8.62 (1 H, s, H-2'), 11.57 (2 H, s, NHCO), *m/z* (EI) 566.3226, (requires C₃₃H₄₀N₇O₂ M+H 566.3243).

15

Example 82

Tetrahydrochloride Salt

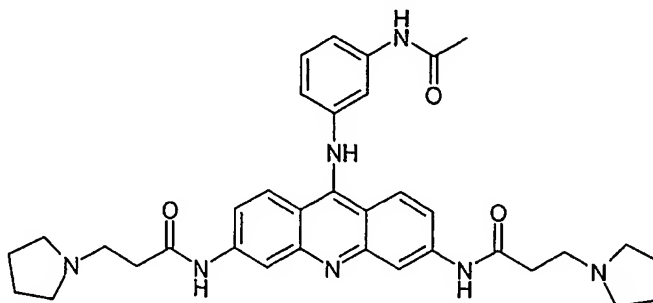
(SB-ACI-13)

- 20 The tetrahydrochloride addition salt, **SB-ACI-13**, of the compound in the previous example, was also prepared by treatment with HCl.

- 116 -

Example 83

N-{9-[(3'-Acetamido)aminophenyl]}-3,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/164**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with *N*-(3-amino-phenyl)-acetamide (0.5 g) according to the general procedure to give the desired product **BSU-SB-36/164** (430 mg, 70%) as a yellow solid.

¹H-NMR (DMSO) δ 1.89-2.07 (11 H, m, N(CH₂CH₂)₂ and CH₃), 3.05-3.10 (8 H, m, N(CH₂CH₂)₂), 3.39-3.53 (8 H, m, COCH₂CH₂N), 6.97-7.00 (1 H, d, J 7.8 Hz, H-6'), 7.34-7.39 (1 H, t, J 7.8 Hz, H-5'), 7.43-7.47 (2 H, d, J 9.4 Hz, H-2, 7), 7.51-7.54 (1 H, d, J 7.8 Hz, H-4'), 7.79 (1 H, s, H-2'), 8.11-8.15 (2 H, d, J 9.4 Hz, H-1, 8), 8.50 (2 H, s, H-4, 5), 10.35 (1 H, s, NH), 11.07 (2 H, s, NH), 11.17 (1 H, s, NH), 11.38 (2 H, s, NH), 14.08 (1 H, s, NH).

15

Example 84

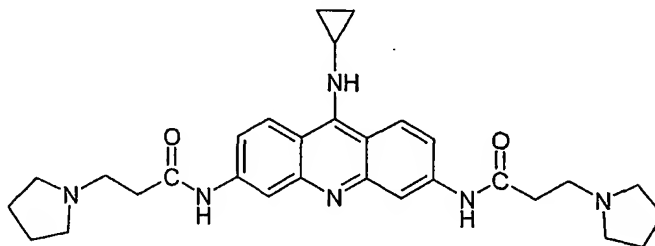
Tetrahydrochloride Salt
(**SB-ACI-14**)

- 20 The tetrahydrochloride addition salt, **SB-ACI-14**, of the compound in the previous example, was also prepared by treatment with HCl.

- 117 -

Example 85

N-[9-(Cyclopropylamino)]-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-13**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (300 mg, 0.6 mmol) was treated with cyclopropylamine (0.43g, 1.8 mmol) according to the general procedure to give the desired product **JM-ACI-13** (290 mg, 70%) as a yellow solid.
- 10 Mp >320 °C, ¹H-NMR (DMSO) δ 0.36 (2 H, m, CH₂), 0.39 (2 H, m, CH₂), 1.70 (8 H, m, N(CH₂CH₂)₂), 2.55 (4 H, m, COCH₂CH₂N), 2.58 (8 H, m, N(CH₂CH₂)₂), 2.84 (4 H, m, COCH₂CH₂N), 2.90 (1 H, m, CH), 7.02 (2 H, m, H-1,8), 7.9 (2 H, m, H-4,5), 8.2 (2 H, m, H-2,7) 10.00 (1 H, s, NHCO), 10.28(2 H, s, NHCO), *m/z* (EI) 515.3160 (C₃₀H₃₉N₆O₂ M+H requires 515.3134).

15

Example 86

Trihydrochloride Salt

(JM-ACI-14)

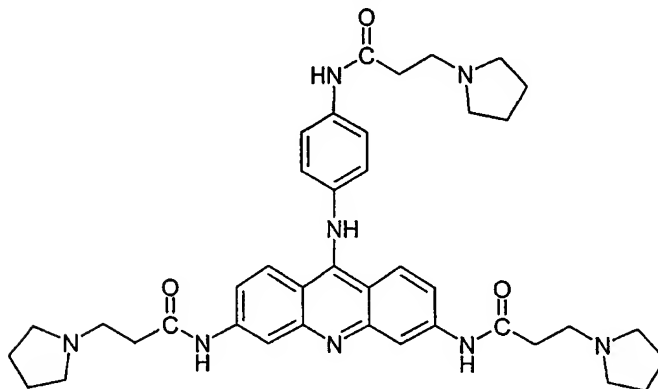
- 20 The trihydrochloride addition salt, **JM-ACI-14**, of the compound in the previous example, was also prepared by treatment with HCl.

- 118 -

Example 87

N-{9-[4'-(3-Pyrrolidin-1-yl-propionylamino)-phenylamino]}-3,6-bis(3-pyrrolidinopropionamido)acridine

(JC-ACI-9a)



3,6-Bisamido-9-chloroacridine **BR-ACO-18** (300 mg, 0.6 mmol) was treated with *N*-(4-aminophenyl)-3-pyrrolidin-1-yl-propionamide (0.43g, 1.8 mmol) according to the general procedure to give the desired product **JC-ACI-9a** (290 mg, 70%) as an orange solid.

Mp 147-149 °C, ¹H-NMR (DMSO) δ 1.74 (12 H, m, N(CH₂CH₂)₂), 2.59 (18H, m, COCH₂CH₂N and N(CH₂CH₂)₂), 2.77 (6H, t, J 6.7 Hz, COCH₂CH₂N), 6.72 (2 H, d, J 8.6 Hz, H-3',5'), 6.97 (2 H, m, H-1,8), 7.54 (2H, d, J 8.6 Hz, H-2',6'), 7.98 (4 H, m, H-2,7 and H-4,5), 10.01 (1 H, s, NH), 10.36 (3 H, s, NHCO). Elemental analysis found for C₄₆H₅₀N₈O₃·H₂O: C 67.56, H 7.32, N 15.48; requires: C 67.77, H 7.39, N 15.81, *m/z* (EI) 691.4070 (C₄₀H₅₁N₇O₂ M+H requires 691.4084).

Example 88

Trihydrochloride Salt

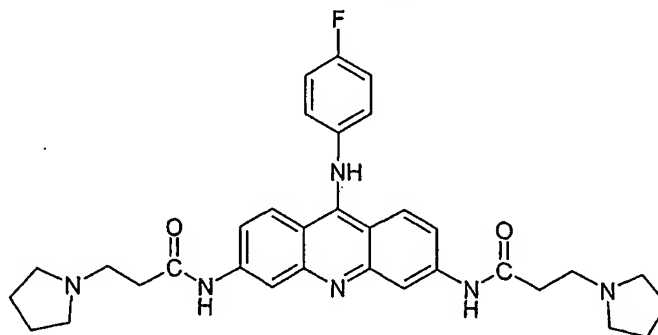
(JC-ACI-9)

The trihydrochloride addition salt, **JC-ACI-9**, of the compound in the previous example was also prepared by treatment with HCl.

- 119 -

Example 89

N-(9-[4'-Fluorophenylamino])-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JC-ACI-3a**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 4-fluoroaniline (0.3 mL) according to the general procedure to give the desired product **JC-ACI-3a** (650 mg, 71%) as a red solid.

- ¹H-NMR (CDCl₃) δ 1.89 (8 H, bs, N(CH₂CH₂)₂), 2.59 (4 H, t, J 5.5 Hz, COCH₂CH₂N), 2.68 (8 H, bs, N(CH₂CH₂)₂), 2.86 (4 H, t, J 5.5 Hz, COCH₂CH₂N),
10 6.80 (4 H, m, H-2,7 and H-3',5'), 6.98 (4 H, m, H-1,8 and H-2',6'), 8.02 (2H, s, H-4,5), 11.57 (2H, s, NHCO), *m/z* (EI) 569.3056 (C₃₃H₃₉FN₆O₂ M+H requires 569.3040).

15

Example 90

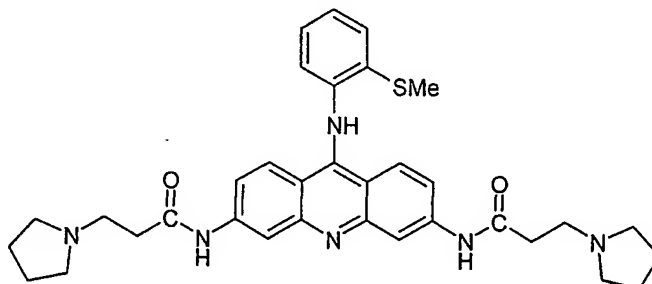
Trihydrochloride Salt
(**JC-ACI-3**)

- The trihydrochloride addition salt, **JC-ACI-3**, of the compound in the previous
20 example was also prepared by treatment with HCl.

- 120 -

Example 91

N-{9-[2'-(Methylsulfanyl)phenylamino]}-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JC-ACI-4a**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (500 mg, 1.0 mmol) was treated with 2-(methylthio)aniline (0.2 mL) according to the general procedure to give the desired product **JC-ACI-4a** (650 mg, 71%) as a red solid.

- Mp >320 °C, ¹H-NMR (DMSO) δ 1.9 (8 H, m, N(CH₂CH₂)₂), 2.39 (3 H, s, SMe),
10 2.42 (8 H, m, N(CH₂CH₂)₂), 2.56 (4 H, m, COCH₂CH₂N), 2.84 (4 H, m, COCH₂CH₂N), 6.14 (1 H, d, J 7.9 Hz, H-4'), 6.30 (1 H, s, H-2'), 6.39 (1 H, d, J 8.1 Hz, H-6'), 7.11 (1 H, dd, J 7.9 Hz 8.1 Hz, H-5'), 7.9 (6 H, m, H-1,2,4,5,7,8), 11.58 (2 H, s, NHCO), *m/z* (EI) 597.3035, (C₃₄H₄₁N₆O₂ M+H requires 597.3012).

15

Example 92

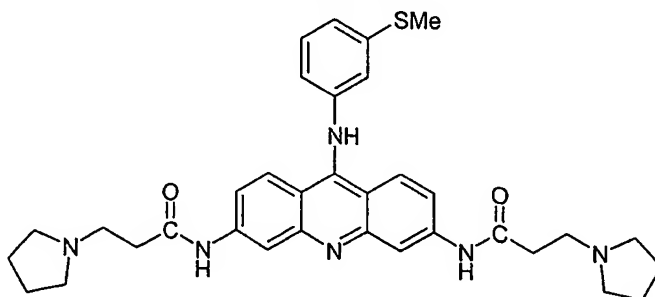
Trihydrochloride Salt
(**JC-ACI-4**)

- The trihydrochloride addition salt, **JC-ACI-4**, of the compound in the previous
20 example was also prepared by treatment with HCl.

- 121 -

Example 93

N-{9-[3'-Methylsulfanyl-phenylamino]}-3,6-bis(3-pyrrolidinopropionamido)acridine
(**JC-ACI-5a**)



- 5 3,6-Bisamido-9-chloroacridine **BR-ACO-18** (800 mg, 1.6 mmol) was treated with 3-(methylthio)aniline (0.4 ml) according to the general procedure to give the desired product **JC-ACI-5a** (650 mg, 71%) as a red solid.

- Mp >320 °C, ¹H-NMR (DMSO) δ 1.9 (8 H, m, N(CH₂CH₂)₂), 2.39 (3 H, s, SMe),
10 2.42 (8 H, m, N(CH₂CH₂)₂), 2.56 (4 H, m, COCH₂CH₂N), 2.84 (4 H, m, COCH₂CH₂N), 6.61 (1 H, m, H-4'), 6.79 (1 H, s, H-2'), 6.85 (1 H, m, H-6'), 7.10 (3 H, m, H-1,8, H-5'), 7.95 (4 H, m, H-2,4,5,7), 11.37 (2 H, s, NHCO), *m/z* (EI) 597.3035 (C₃₄H₄₁N₆O₂ M+H requires 597.3012).

15

Example 94

Trihydrochloride Salt

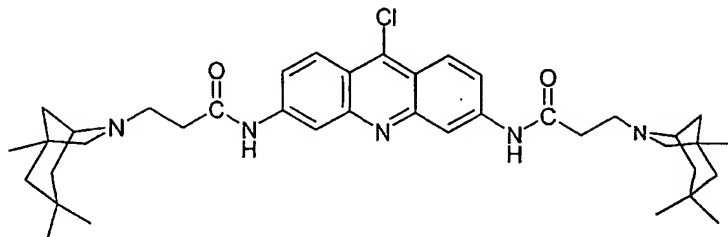
(JC-ACI-5)

- The trihydrochloride addition salt, **JC-ACI-5**, of the compound in the previous
20 example was also prepared by treatment with HCl.

- 122 -

Example 95

9-Chloro-3,6-bis[(1,3,3-trimethyl-6-azabicyclo[3.2.1]-octanamino)propionamido]-
acridine

(JH-ACI-33)

5

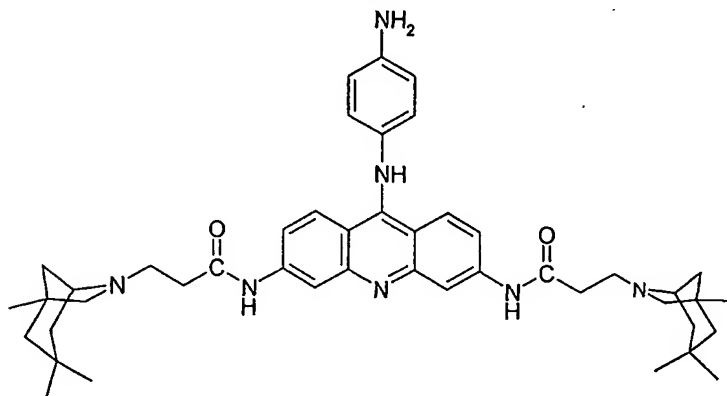
A suspension of the 3,6-bisamido-9(10*H*)-acridone **JH-ACO-31** (4.0 g, 6.25 mmol) in POCl₃ (75 mL) was refluxed for 2 hr, after cooling to 0 °C the suspension was filtered and the collected solid washed with toluene (2 x 50 mL), and Et₂O (2 x 100 mL). The product was collected and dissolved in CHCl₃ (100 mL) and washed
10 with dilute ammonia solution (2 x 75 mL), brine (100 mL), dried and treated with charcoal. Evaporation under reduced pressure provided **JH-ACI-31** (3.1 g, 77%) as a yellow/green solid.

¹H-NMR (CDCl₃) δ 0.88 (6H, s, CH₃), 1.08 (6H, s, CH₃), 1.35 (4H, m, CH₂) 1.47
15 (6H, s, CH₃), 1.52 (4H, m, CH₂), 1.65-1.75 (4H, m, CH₂), 2.22 (2H, m, CH), 2.48 (4H, m, COCH₂), 2.80-2.89 (4H, m, COCH₂CH₂N), 2.92 (6 H, s, N(CH₃)₂), 3.20-3.30 (4H, m, CH₂), 7.97 (2H, d, J 9.4 Hz, H-2,7), 8.10 (2H, s, H-4,5), 8.33 (2H, d, J 9.4 Hz, H-1,8), 11.82 (2H, s, NHCO).

- 123 -

Example 96

N-[9-[4'-(Amino)phenylamino]]-3,6-bis[(1,3,3-trimethyl-6-azabicyclo[3.2.1]-octanamino)propionamido]-acridine

(JH-ACI-100)

5

3,6-Bisamido-9-chloroacridine **JH-ACI-33** (1.0 g, 1.5 mmol) was treated 1,4-phenylenediamine (700 mg) according to the general procedure to give the desired product **JH-ACI-100** (500 mg, 45%) as a brown solid.

- 10 NMR (DMSO) δ 0.84 (6H, s, CH_3), 1.02 (6H, s, CH_3), 1.25 (4H, m, CH_2) 1.07 (6H, s, CH_3), 1.21 (4H, m, CH_2), 1.34 (4H, m, CH_2), 2.34 (2H, m, CH), 2.63 (4H, t, COCH_2), 3.07 (4H, m, $\text{COCH}_2\text{CH}_2\text{N}$), 3.20–3.30 (4H, m, CH_2), 5.48 (2 H, sbr, NH_2), 6.66 (2 H, d, J 8.0 Hz, ArH-3'5'), 7.05 (2 H, d, J 8.0 Hz, ArH-2'6'), 7.31 (2 H, d, J 7.7 Hz, H-1,8), 8.06 (2 H, d, J 7.7 Hz, H-2,7), 8.4 (2 H, s, H-4,5), 10.88 (2 H, s, NHCO),
- 15 10.76 (2 H, s, NHCO), m/z [EI] (relative intensity%) 731 ([M+H], 100), 577 (M - $\text{C}_{10}\text{H}_{18}\text{N}$, 10), 522 (M - $\text{C}_{13}\text{H}_{23}\text{NO}$, 15), 316 (M - $\text{C}_{26}\text{H}_{46}\text{N}_2\text{O}_2$, 11).

Example 97

Trihydrochloride Salt

(JH-ACI-101)

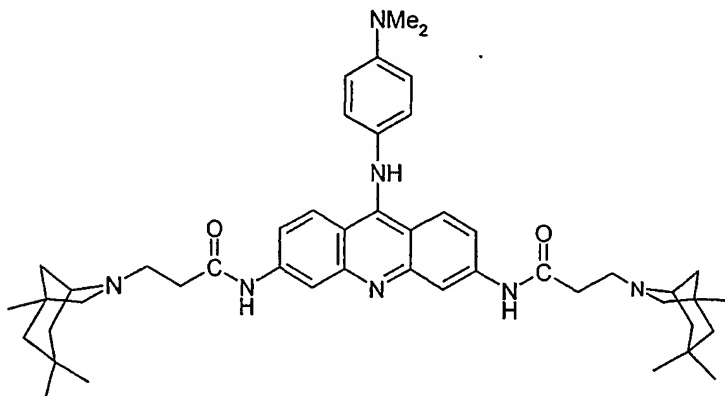
20

The trihydrochloride addition salt, **JH-ACI-101**, of the compound in the previous example, was also prepared by treatment with HCl.

- 124 -

Example 98

N-{9-[4'-(*N,N*-Dimethylamino)phenylamino]}-3,6-bis[(1,3,3-trimethyl-6-azabicyclo[3.2.1]-octanamino)propionamido]-acridine

(JH-ACI-102)

5

3,6-Bisamido-9-chloroacridine **JH-ACI-33** (1.0 g, 1.5 mmol) was treated *N,N*-dimethyl-1,4-phenylenediamine (700 mg) according to the general procedure to give the desired product **JH-ACI-102** (715 mg, 62%) as a brown solid.

- 10 Mp > 300 °C ¹H-NMR (CDCl₃) δ 0.88 (6H, s, CH₃), 1.08 (6H, s, CH₃), 1.35 (4H, m, CH₂) 1.47 (6H, s, CH₃), 1.52 (4H, m, CH₂), 1.65-1.75 (4H, m, CH₂), 2.22 (2H, m, CH), 2.48 (4H, m, COCH₂), 2.80–2.89 (4H, m, COCH₂CH₂N), 2.92 (6 H, s, N(CH₃)₂), 3.20–3.30 (4H, m, CH₂), 6.73 (2 H, d, J 8.8 Hz, H-3',5'), 6.86 (2 H, d, J 8.8 Hz, H-2',6'), 7.97 (6 H, m, H-1,2,4,5,7,8), 10.76 (2 H, s, NHCO), m/z [EI]
- 15 (relative intensity%) 759 ([M+H], 100), 605 (M-C₁₀H₁₉N, 25), 577 (22), 551 (M-C₁₃H₂₂NO, 23), 453 (M-C₂₀H₃₆N₂, 10), 370 (M-C₂₅H₄₁N₂O).

Example 99

Trihydrochloride Salt

(JH-ACI-103)

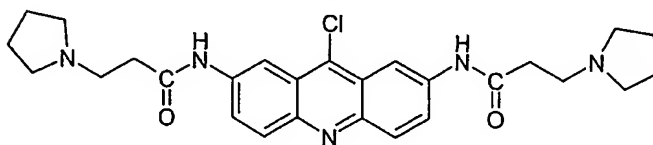
20

The trihydrochloride addition salt, **JH-ACI-103**, of the compound in the previous example, was also prepared by treatment with HCl.

- 125 -

GROUP E: 2,7,9-ACRIDINES**Example 100**

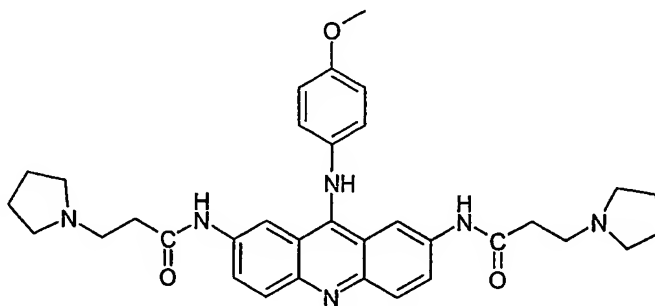
9-Chloro-2,7-bis(3-pyrrolidinopropionamido)acridine

(JM-ACI-43)

2,7-Bisamidoacridone **BR-ACO-16** (1 g, 2.1 mmol) was treated with refluxing POCl₃ for 3 hr. The reaction was cooled, and anhydrous diethyl ether was added to precipitate product. Solids were filtered from solution to give the desired product

JM-ACI-43 (750 mg, 72%) as a yellow solid.

Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.91 (8 H, m, N(CH₂CH₂)₂), 2.56 (4 H, t, J 5.8 Hz, COCH₂CH₂N), 2.69 (8 H, m, N(CH₂CH₂)₂), 2.86 (4 H, t, J 5.8 Hz, COCH₂CH₂N), 7.64 (2 H, dd, J 9.3 Hz, J 2.0 Hz, H-3,6), 8.05 (2 H, d, J 9.3 Hz, H-4,5), 8.64 (2 H, d, J 2.0 Hz, H-1,8), 11.78 (2 H, s, NHCO), *m/z* (EI) 494.2342 (C₂₇H₃₃ClN₅O₂ M+H requires 494.2323).

Example 101*N*-[9-(4'-Methoxyphenylamino)]-2,7-bis(3-pyrrolidinopropionamido)acridine**(JM-ACI-10)**

2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with *p*-anisidine (0.5 mL) according to the general procedure to give the desired product **JM-ACI-10** (100 mg, 52%) as a bright orange solid.

- 126 -

Mp >320 °C, $^1\text{H-NMR}$ (DMSO) δ 1.66 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.50 (12 H, m, $\text{COCH}_2\text{CH}_2\text{N}$, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.71 (4 H, t, J 6.8 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 3.65 (3 H, s, OCH_3), 6.62 (2 H, d, J 8.6 Hz, H-3',5'), 6.74 (2 H, d, J 8.6 Hz, H-2',6'), 7.92 (2 H, m, J 9.3 Hz, H-3,6), 8.01 (2 H, d, J 9.3 Hz, H-4,5), 8.33 (2 H, m, H-1,8), 10.36 (2 H, s, NHCO), m/z (EI) 581.3260 ($\text{C}_{34}\text{H}_{41}\text{N}_6\text{O}_3$ M+H requires 581.3240).

Example 102

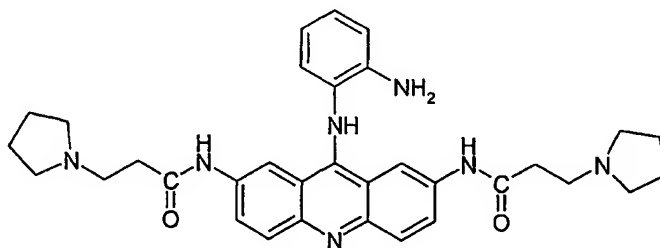
Trihydrochloride Salt

(JM-ACI-11)

The trihydrochloride addition salt, **JM-ACI-10**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 103

N-[9-(2'-Aminophenylamino)]-2,7-bis(3-pyrrolidinopropionamido)acridine
(JM-ACI-29)



2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with 1,2-phenylenediamine (70 mg) according to the general procedure to give the desired product **JM-ACI-29** (90 mg, 53%) as a dark red solid.

Mp >320 °C, $^1\text{H-NMR}$ (CDCl_3) δ 1.79 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.46 (4 H, t, J 5.8 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 2.58 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.77 (4 H, t, J 5.8 Hz, $\text{COCH}_2\text{CH}_2\text{N}$), 6.39 (1 H, m, H-1'), 6.48 (1 H, m, H-4'), 6.82 (2 H, m, H-1',2'), 7.55 (2 H, dd, J 9.3 Hz, J 2.3 Hz, H-3,6), 7.98 (2 H, d, J 9.3 Hz, H-4,5), 8.18 (2 H, d, J 2.3 Hz, H-1,8), 11.26 (2 H, s, NHCO), m/z (EI) 566.3219 ($\text{C}_{33}\text{H}_{40}\text{N}_7\text{O}_2$ M+H requires 566.3243).

- 127 -

Example 104

Trihydrochloride Salt

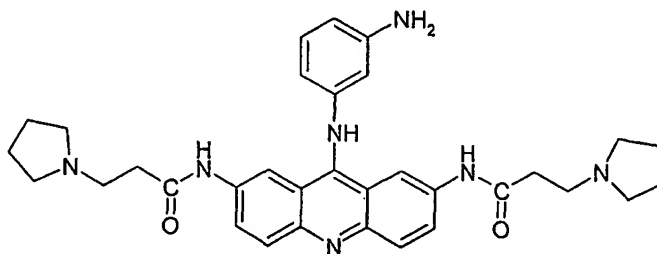
(JM-ACI-30)

- 5 The trihydrochloride addition salt, **JM-ACI-29**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 105

10 *N*-[9-(3'-Aminophenylamino)]-2,7-bis(3-pyrrolidinopropionamido)acridine

(JM-ACI-31)



2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with 1,3-phenylenediamine (70 mg) according to the general procedure to give **JM-ACI-31** (100 mg, 59%) as brown solid.

15

Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.75 (8 H, m, N(CH₂CH₂)₂), 2.45 (4 H, t, J 5.8 Hz, COCH₂CH₂N), 2.56 (8 H, m, N(CH₂CH₂)₂), 2.76 (4 H, t, J 5.8 Hz, COCH₂CH₂N), 5.96 (1 H, s, H-2'), 6.04 (1 H, d, J 7.4 Hz, H-4'), 6.12 (1 H, d, J 8.6 Hz, H-6'), 6.85 (2 H, dd, J 8.6 Hz, J 5.75 Hz, H-5'), 7.69 (2 H, dd, J 9.3 Hz, J 2.25 Hz, H-3,6), 8.00 (2 H, d, J 9.3 Hz, H-4,5), 8.12 (2 H, d, J 2.3 Hz, H-1,8), 11.52 (2 H, s, NHCO), *m/z* (EI) 566.3249 (C₃₃H₄₀N₇O₂ M+H requires 566.3243).

20

Example 106

Trihydrochloride Salt

(JM-ACI-32)

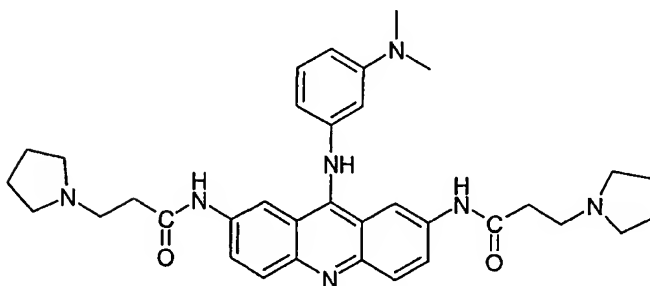
25

The trihydrochloride addition salt, **JM-ACI-31**, of the compound in the previous example, was also prepared by treatment with HCl.

- 128 -

Example 107

N-{9-[3'-(*N,N*-Dimethylamino)phenylamino]}-2,7-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-33**)



2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with *N,N*-dimethyl-1,3-phenylenediamine (85 mg) according to the general procedure to give the desired product **JM-ACI-33** (70 mg, 39%) as a dark brown solid.

10

Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.75 (8 H, m, N(CH₂CH₂)₂), 2.53 (4 H, t, J 6.0 Hz, COCH₂CH₂N), 2.64 (8 H, m, N(CH₂CH₂)₂), 2.75 (6 H, s, N(CH₂)₂), 2.85 (4 H, t, J 6.0 Hz, COCH₂CH₂N), 6.04 (1 H, m, J 7.8 Hz, H-4'), 6.23 (2 H, m, H-2',6'), 6.92 (1 H, dd, J 7.3 Hz, J 7.3 Hz, H-5'), 7.81 (2 H, dd, J 9.3 Hz, J 2.3 Hz, H-3,6), 8.02 (2 H, d, J 9.3 Hz, H-4,5), 8.10 (2 H, d, J 2.3 Hz, H-1,8), 11.28 (2 H, s, NHCO), *m/z* (EI) 594.3572 (C₃₅H₄₄N₇O₂ M+H requires 594.3556).

15

Example 108

Trihydrochloride Salt

(JM-ACI-34)

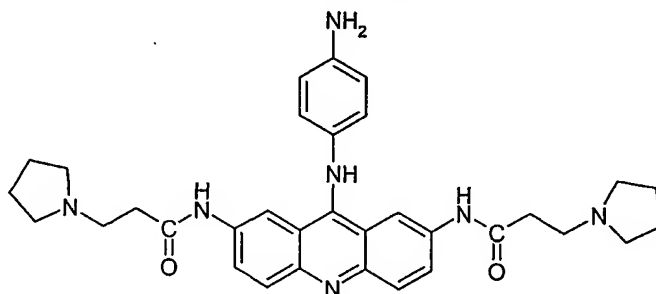
20

The trihydrochloride addition salt, **JM-ACI-33**, of the compound in the previous example, was also prepared by treatment with HCl.

- 129 -

Example 109

N-[9-(4'-Aminophenylamino)]-2,7-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-35**)



5

2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with 1,4-phenylenediamine (70 mg) according to the general procedure to give the desired product **JM-ACI-35** (55 mg, 32%) as a dark red solid.

- 10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.79 (8 H, m, N(CH₂CH₂)₂), 2.45 (4 H, t, J 6.0 Hz, COCH₂CH₂N), 2.57 (8 H, m, N(CH₂CH₂)₂), 2.76 (4 H, t, J 6.0 Hz, COCH₂CH₂N), 6.48 (2H, d, J 8.8 Hz, H-3',5'), 6.66 (2H, d, J 8.8 Hz, H-2',6'), 7.60 (2 H, dd, J 9.0 Hz, J 2.3 Hz, H-3,6), 7.98 (2 H, d, J 9.0 Hz, H-4,5), 8.19 (2 H, d, J 2.3 Hz, H-1,8), 11.43 (2 H, s, NHCO), *m/z* (EI) 566.3225 (C₃₃H₄₀N₇O₂ M+H requires 566.3243).

15

Example 110

Trihydrochloride Salt

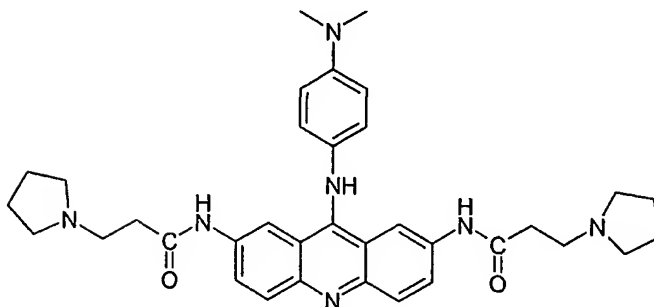
(JM-ACI-36)

- 20 The trihydrochloride addition salt, **JM-ACI-35**, of the compound in the previous example, was also prepared by treatment with HCl.

- 130 -

Example 111

N-{9-[4'-(*N,N*-dimethylamino)phenylamino]}-2,7-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-37**)



5

2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with *N,N*-dimethyl-1,4-phenylenediamine (90 mg) according to the general procedure to give the desired product **JM-ACI-37** (50 mg, 28%) as a dark brown solid.

- 10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.77 (8 H, m, N(CH₂CH₂)₂), 2.47 (4 H, t, J 5.7 Hz, COCH₂CH₂N), 2.54 (8 H, m, N(CH₂CH₂)₂), 2.78 (4 H, t, J 5.75 Hz, COCH₂CH₂N), 2.82 (6 H, s, N(CH₂)₂), 6.57 (2 H, d, J 9.0 Hz, H-3',5'), 6.77 (2 H, d, J 9.0 Hz, H-2',6'), 7.70 (2 H, dd, J 9.2 Hz, J 2.2 Hz, H-3,6), 8.01 (2 H, d, J 9.2 Hz, H-4,5), 8.12 (2 H, d, J 2.2 Hz, H-1,8), 11.41 (2 H, s, NHCO), *m/z* (EI) 594.3572 (C₃₅H₄₄N₇O₂).
- 15 M+H requires 594.3556).

Example 112

Trihydrochloride Salt

(JM-ACI-38)

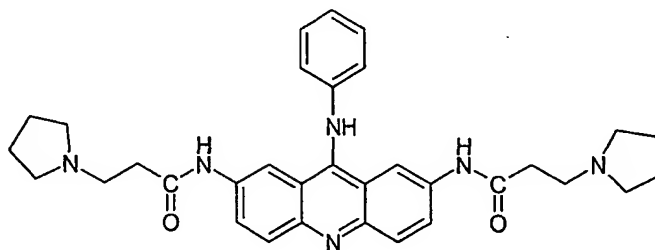
20

The trihydrochloride addition salt, **JM-ACI-37**, of the compound in the previous example, was also prepared by treatment with HCl.

- 131 -

Example 113

N-(9-Phenylamino)-2,7-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-39**)



- 5 2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with aniline (0.5 ml) according to the general procedure to give the desired product **JM-ACI-39** (120 mg, 72%) as a bright red solid.
- 10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.74 (8 H, m, N(CH₂CH₂)₂), 2.46 (4 H, t, J 5.7 Hz, COCH₂CH₂N), 2.55 (8 H, m, N(CH₂CH₂)₂), 2.76 (4 H, t, J 5.7 Hz, COCH₂CH₂N), 6.4 (1 H, m, H-1'), 6.7 (1 H, d, J 7.5 Hz, H-4'), 6.83 (2 H, m, H-3',5'), 7.10 (2 H, m, H-2',6'), 7.69 (2 H, dd, J 9.3 Hz, J 2.3 Hz, H-3,6), 8.04 (2 H, d, J 9.3 Hz, H-4,5), 8.14 (2 H, d, J 2.3 Hz, H-1,8), 11.56 (2 H, s, NHCO), *m/z* (EI) 551.3153 (requires C₃₃H₃₉N₆O₂ M+H 551.3134).

15

Example 114

Trihydrochloride Salt

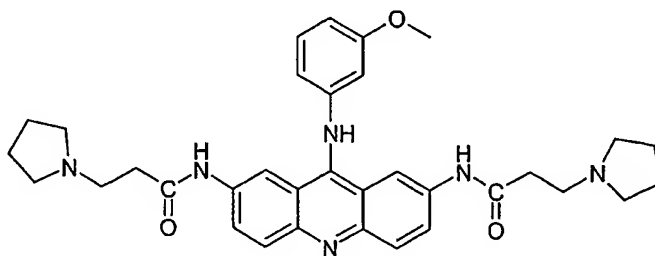
(JM-ACI-40)

- 20 The trihydrochloride addition salt, **JM-ACI-39**, of the compound in the previous example, was also prepared by treatment with HCl.

- 132 -

Example 115

N-[9-(3'-Methoxyphenylamino)]-2,7-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-41**)



- 5 2,7-Bisamido-9-chloroacridine **BR-ACO-16** (200 mg, 0.4 mmol) was treated with *m*-anisidine (0.5mL) according to the general procedure to give the desired product **JM-ACI-41** (100 mg, 43%) as an orange solid.

- Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.79 (8 H, m, N(CH₂CH₂)₂), 2.53 (4 H, t, J 5.3 Hz, COCH₂CH₂N), 2.62 (8 H, m, N(CH₂CH₂)₂), 2.83 (4 H, t, J 5.3 Hz, COCH₂CH₂N),
10 3.64 (3 H, s, OCH₃), 6.36 (3 H, m, H-2',4',6'), 7.3 (1 H, m, H-5'), 7.80 (2 H, m, J 9.3 Hz, H-3,6), 8.04 (2 H, d, J 9.3 Hz, H-4,5), 8.16 (2 H, m, H-1,8), 11.60 (2 H, s, NHCO), *m/z* (EI) 581.3247 (C₃₄H₄₁N₆O₃ M+H requires 581.3240).

15

Example 116

Trihydrochloride Salt

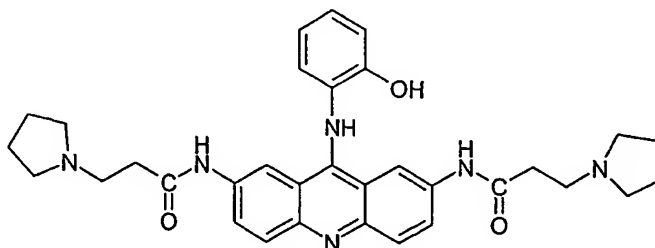
(JM-ACI-42)

- The trihydrochloride addition salt, **JM-ACI-41**, of the compound in the previous
20 example, was also prepared by treatment with HCl.

- 133 -

Example 117

N-[9-(2'-Hydroxyphenylamino)]-2,7-bis(3-pyrrolidinopropionamido)acridine
(**JM-ACI-45**)



- 5 2,7-Bisamido-9-chloroacridine **BR-ACO-16** (150 mg, 0.3 mmol) was treated with 1,2-aminophenol (50 mg) according to the general procedure to give the desired product **JM-ACI-45** (100 mg, 59%) as a dark red solid.

- 10 Mp >320 °C, ¹H-NMR (CDCl₃) δ 1.80 (8 H, m, N(CH₂CH₂)₂), 2.57 (4 H, t, J 6 Hz, COCH₂CH₂N), 2.63 (8 H, m, N(CH₂CH₂)₂), 2.86 (4 H, t, J 6.0 Hz, COCH₂CH₂N), 6.45 (1 H, m, H-2'), 6.59 (1 H, m, H-3'), 6.75 (1 H, m, H-4'), 6.94 (1 H, m, H-5'), 7.73 (2 H, m, J 9.3 Hz, J 2.25 Hz, H-3,6), 8.00 (2 H, d, J 9.3 Hz, H-4,5), 8.16 (2 H, d, J 2.25 Hz, H-1,8), 11.30 (2 H, s, NHCO), *m/z* (EI) 567.3067 (C₃₃H₄₀N₇O₂ M+H requires 567.3084).

15

Example 118

Trihydrochloride Salt

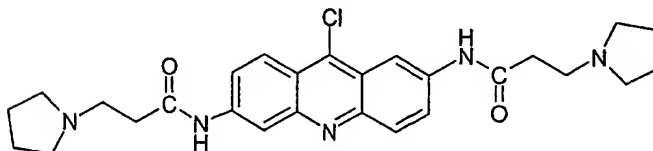
(JM-ACI-46)

- 20 The trihydrochloride addition salt, **JM-ACI-45**, of the compound in the previous example, was also prepared by treatment with HCl.

- 134 -

GROUP F: 2,6,9-ACRIDINES**Example 119**

9-chloro-2,6-bis(3-pyrrolidinopropionamido)acridine
(JH-ACI-98)



A suspension of 2,6-bis(3-pyrrolidinopropionamido)acridone **AR-ACO-10** (2.0 g, 4.2 mmol) in CHCl_3 (40 mL) was treated with phosphorus pentachloride (0.9 g, 4.2 mmol), followed by cautious addition of phosphorus oxychloride (50 mL). This suspension was stirred at room temp. for 30 min and brought to a gentle reflux over 1 hr. Gentle reflux was maintained for 26 hr. The reaction mixture was cooled to rt then slowly dropped onto ice (~600 mL) over 10 min. The aqueous mixture was made basic to pH 7/8 with ammonia whilst maintaining a temp. <25 °C. The aqueous layer was extracted with CHCl_3 (5 × 200 mL). The organic extracts were combined, washed with brine (200 mL), dried (Na_2SO_4) and concentrated. The resulting solid was triturated with diethyl ether (30 mL) to give the desired product (1.3 g, 62%) as a light brown solid.

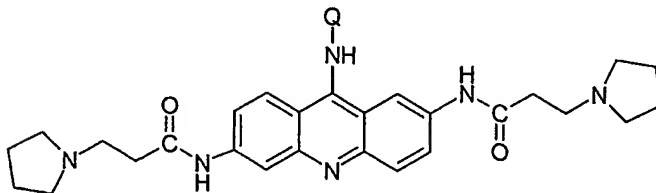
$^1\text{H-NMR}$ (CDCl_3) δ 1.97-1.98 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.61-2.66 (4 H, m, $\text{COCH}_2\text{CH}_2\text{N}$), 2.75-2.76 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.90-2.96 (4 H, m, $\text{COCH}_2\text{CH}_2\text{N}$), 7.66-7.70 (1 H, d, J 9.3 Hz and 2.2 Hz, H-3/7), 7.92-7.96 (1 H, d, J 9.3 and 2.2 Hz, H-3/7), 8.08-8.11 (1 H, d, J 9.3 Hz, H-4/8), 8.17-8.18 (1 H, m, H-1/5), 8.31-8.35 (1 H, d, J 9.3 Hz, H-4/8), 8.75-8.76 (1 H, m, H-1/5), 11.72 (2 H, s, NHCO).

25

- 135 -

Example 120

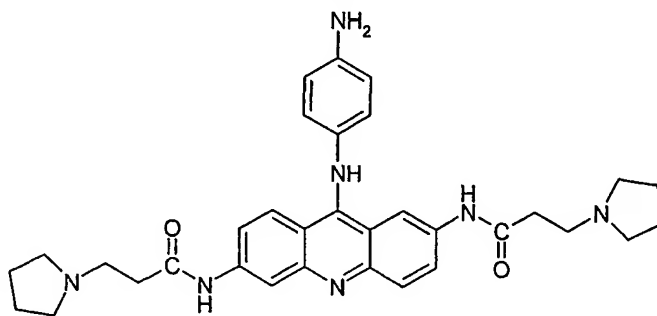
9-Substitution, 2,6,9-Derivatives, General Procedure



To a vigorously stirred solution of **JH-ACI-98** in CHCl_3 was added dropwise a
 5 solution of the proposed amine, Q-NH_2 (e.g., $\text{NH}_2(\text{CH}_2)_p\text{NH}_2$, substituted anilines),
 for example, in CHCl_3 . This solution was stirred for a further 2-5 hr, the solvent was
 removed under reduced pressure, the resultant compound was purified by flash
 column chromatography. The eluent used for 9-aryl substituents was 100% CHCl_3
 (NEt_3) to 30% $\text{MeOH}/\text{CHCl}_3$ (NEt_3). The eluent used for 9-alkyl substituents was
 10 100% CHCl_3 (NEt_3) to 5% NEt_3 in MeOH .

Example 121

N-{9-[4'-(Amino)phenylamino]}-2,6-bis(3-pyrrolidinopropionamido)acridine
 (**JH-ACI-104**)



15

2,6-Bisamido-9-chloroacridine **JH-ACI-98** (500 mg, 1.0 mmol) was treated with
 1,4-phenylenediamine (0.5 mL) according to the general procedure to give the
 desired product **JH-ACI-104** (400 mg, 88%) as a brown solid.

20 Mp >320 °C, $^1\text{H-NMR}$ (CDCl_3) δ 1.83 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.55 (4 H, m,
 $\text{COCH}_2\text{CH}_2\text{N}$), 2.58 (8 H, m, $\text{N}(\text{CH}_2\text{CH}_2)_2$), 2.84 (4 H, m, $\text{COCH}_2\text{CH}_2\text{N}$), 6.61 (2 H,
d, J 8.7 Hz, ArH-3',5'), 6.66 (2 H, d, J 8.7 Hz, ArH-2',6'), 7.5-8.0 (6 H, m, H-
1,3,4,5,7,8) 10. (1 H, s, NHCO), 10.89 (1 H, s, NHCO), m/z (EI) 566.3219

- 136 -

(C₃₃H₄₄N₇O₂ M+H requires 566.3243).Example 122

Trihydrochloride Salt

(JH-ACI-105)

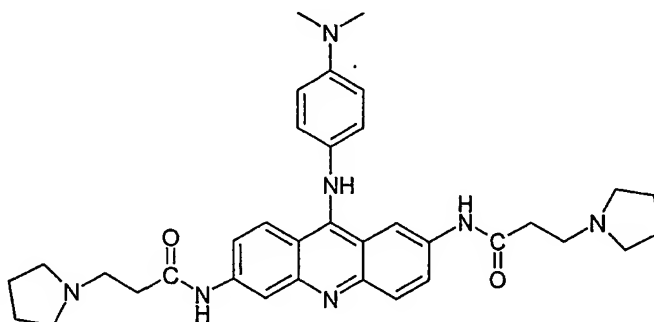
5

The trihydrochloride addition salt, **JH-ACI-105**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 123

N-{9-[4'-(*N,N*-Dimethyl)phenylamino]}-2,6-bis(3-pyrrolidinopropionamido)acridine
(BSU-SB-36/188)

10



2,6-Bisamido-9-chloroacridine **JH-ACI-98** (500 mg, 1.0 mmol) was treated with
15 4-*N,N*-dimethylaminoaniline (0.4 g) according to the general procedure to give the
desired product **BSU-SB-36/188** (210 mg, 36%) as a dark brown solid.

¹H-NMR (DMSO) δ 1.87-1.92 (8 H, m, N(CH₂CH₂)₂), 2.38-2.59 (4 H, m, COCH₂CH₂N), 2.61-2.80 (8 H, m, N(CH₂CH₂)₂), 2.87-2.92 (10 H, m, COCH₂CH₂N and N(CH₃)₂), 6.64-6.67 (2 H, d, J 9.0 Hz, H-2', 6' or H-3', 5'), 6.91-6.94 (2H, d, J 9.0 Hz, H-2', 6' or H-3', 5'), 7.49-7.52 (1 H, m, J 9.0 Hz, acridine), 7.60-7.64 (1 H, m, acridine), 7.73-7.76 (1 H, m, acridine) 7.91-7.92 (2 H, m, acridine), 8.40 (1 H, s, acridine) 11.33 (1 H, s, NHCO), 11.53 (1 H, s, NHCO).

20

- 137 -

Example 124

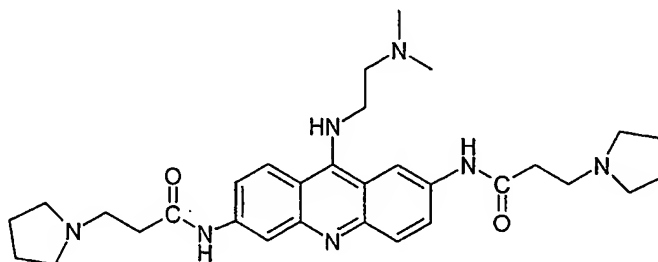
Tetrahydrochloride Salt

(SB-ACI-18)

- 5 The tetrahydrochloride addition salt, **SB-ACI-18**, of the compound in the previous example, was also prepared by treatment with HCl.

Example 125*N*-{9-[2-(*N,N*-Dimethyl)ethylamino]}-2,6-bis(3-pyrrolidinopropionamido)acridine

10

(BSU-SB-36/190)

2,6-Bisamido-9-chloroacridine **JH-ACI-98** (500 mg, 1.0 mmol) was treated with *N,N*-dimethylethylamine (0.33 mL) according to the general procedure to give the desired product **BSU-SB-36/190** (410 mg, 75%) as a brown hygroscopic solid.

15

¹H-NMR (CDCl₃) δ 1.95 (8 H, m, N(CH₂CH₂)₂), 2.39 (6 H, s, CH₃), 2.61-2.67 (6 H, m, COCH₂CH₂N and HNCH₂CH₂N), 2.72 (8 H, s, N(CH₂CH₂)₂), 2.88-2.94 (4 H, m, COCH₂CH₂N), 3.91-3.96 (2 H, m, HNCH₂CH₂N), 7.32-7.33 (1 H, m, H-3/7), 7.78-7.79 (1H, m, H-3/7), 7.93-8.00 (2 H, m, H-8, 1), 8.06-8.10 (1 H, m, J 9.4 Hz, H-4),
20 8.96-8.97 (1 H, m, H-5), 11.54-11.62 (2 H, s, NHCO).

Example 126

Tetrahydrochloride Salt

(SB-ACI-19)

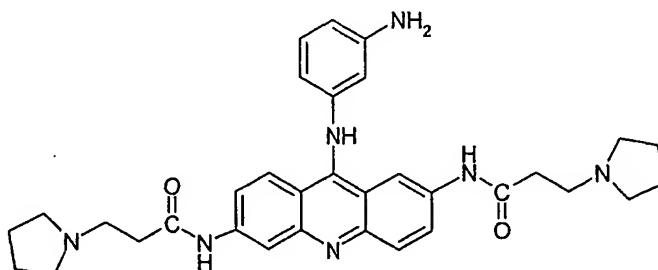
25

The tetrahydrochloride addition salt, **SB-ACI-19**, of the compound in the previous example, was also prepared by treatment with HCl.

- 138 -

Example 127

N-[9-(3'-Aminophenylamino)]-2,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/194**)



- 5 2,6-Bisamido-9-chloroacridine **JH-ACI-98** (500 mg, 1.0 mmol) was treated with 1,3-phenylenediamine (0.32 g) according to the general procedure to give the desired product **BSU-SB-36/194** (110 mg, 19%) as an orange solid.

- ¹H-NMR (CDCl₃) δ 1.89-1.93 (8 H, m, N(CH₂CH₂)₂), 2.57-2.64 (4 H, m, COCH₂CH₂N), 2.73-2.79 (8 H, m, N(CH₂CH₂)₂), 2.90-2.94 (4 H, m, COCH₂CH₂N),
10 6.13 (1 H, s, H-2'), 6.25-6.29 (2 H, m, H-4', 6'), 6.96-7.02 (1 H, t, J 7.9 Hz, H-5'), 7.52-7.62 (1 H, m, H-3, 5 or 4, 8), 7.65-7.66 (1 H, m, H-3, 5 or 4, 8), 7.87-7.91 (1 H, m, H-3, 5 or 4, 8), 7.96-8.00 (1 H, m, H-3, 5 or 4, 8), 8.11-8.12 (1 H, m, H-1/5), 8.39-8.40 (1 H, m, H-1/5), 11.37 (1 H, s, NHCO), 11.52 (1 H, s, NHCO).

15

Example 128

Trihydrochloride Salt

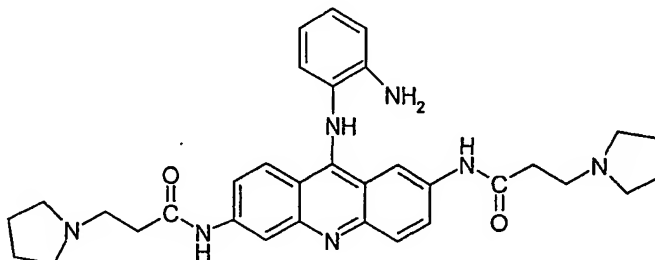
(SB-ACI-17)

- 20 The trihydrochloride addition salt, **SB-ACI-17**, of the compound in the previous example, was also prepared by treatment with HCl.

- 139 -

Example 129

N-[9-(2'-Aminophenylamino)]2,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/202**)



- 5 2,6-Bisamido-9-chloroacridine **AR-ACO-10** (500 mg, 1.0 mmol) was treated with 1,3-phenylenediamine (0.32 g) according to the general procedure to give the desired product **BSU-SB-36/202** (400 mg, 70%) as an orange solid.

- ¹H-NMR (CDCl₃) δ 1.86-1.88 (8 H, m, N(CH₂CH₂)₂), 2.53-2.57 (4 H, m, COCH₂CH₂N), 2.60-2.69 (8 H, m, N(CH₂CH₂)₂), 2.82-2.87 (4 H, t, J 5.8 Hz, COCH₂CH₂N), 6.55 (2 H, m, H-3'/4'/5'/6'), 6.83-6.95 (2 H, m, H-3'/4'/5'/6'), 7.11 (1 H, m), 7.59-7.71 (3 H, m), 7.95 (1 H, m), 8.25 (1 H, s), 11.13 (1 H, s, NHCO), 11.48 (1 H, s, NHCO).
- 10

15

Example 130

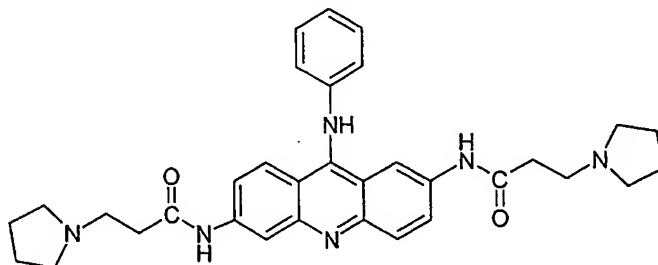
Trihydrochloride Salt
(**SB-ACI-16**)

- The trihydrochloride addition salt, **SB-ACI-16**, of the compound in the previous
20 example, was also prepared by treatment with HCl.

- 140 -

Example 131

N-[9-(Phenylamino)]-2,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/196**)



- 5 2,6-Bisamido-9-chloroacridine **AR-ACO-10** (500 mg, 1.0 mmol) was treated with phenylamine (0.3 mL) according to the general procedure to give the desired product **BSU-SB-36/196** (240 mg, 44%) as an orange solid;

- ¹H-NMR (CDCl₃) δ 1.86-1.92 (8 H, m, N(CH₂CH₂)₂), 2.55-2.62 (4 H, m, COCH₂CH₂N), 2.68-2.72 (8 H, m, N(CH₂CH₂)₂), 2.985-2.92 (4 H, m, COCH₂CH₂N), 6.82-6.85 (2 H, d, J 8.6 Hz, H-2, 6), 6.90-6.96 (1 H, t, H-3), 7.18-7.24 (2 H, dd, H-3, 5), 7.55-7.66 (2 H, m, J 9.3 and 2.2 Hz, H-3, 6), 7.84-7.88 (1 H, d, J 9.3 Hz, H-4/7), 7.95-7.99 (1 H, d, J 9.3 Hz, H-4/7), 8.08 (1 H, m, H-1/5), 8.37 (1 H, m, H-1/5), 11.46 (1 H, s, NHCO), 11.59 (1 H, s, NHCO).

15

Example 132

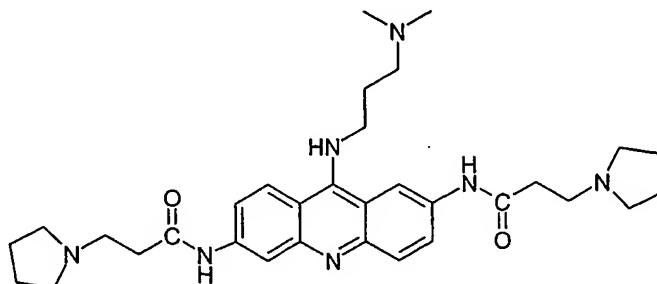
Trihydrochloride Salt
(**SB-ACI-22**)

- 20 The trihydrochloride addition salt, **SB-ACI-22**, of the compound in the previous example, was also prepared by treatment with HCl.

- 141 -

Example 133

N-{9-[3-(*N,N*-Dimethyl)propylamino]}-2,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/198**)



- 5 2,6-Bisamido-9-chloroacridine **AR-ACO-10** (500 mg, 1.0 mmol) was treated with *N,N*-dimethylpropylamino (0.4 mL) according to the general procedure to give the desired product **BSU-SB-36/198** (210 mg, 38%) as a yellow solid.

¹H-NMR (CDCl₃) δ 1.92-1.95 (10 H, m, N(CH₂CH₂)₂ and HNCH₂CH₂CH₂N), 2.39 (6
10 H, s, N(CH₃)₂), 2.58-2.66 (6 H, m, COCH₂CH₂N and HNCH₂CH₂CH₂N), 2.71 (8 H, s, N(CH₂CH₂)₂), 2.87-2.93 (4 H, m, COCH₂CH₂N), 4.12-4.17 (2 H, m, HNCH₂CH₂CH₂N), 7.70 (1 H, m), 7.88-8.07 (4 H, m), 8.96 (1 H, m), 11.48 (1 H, s, NHCO), 11.65 (1 H, s, NHCO).

15

Example 134

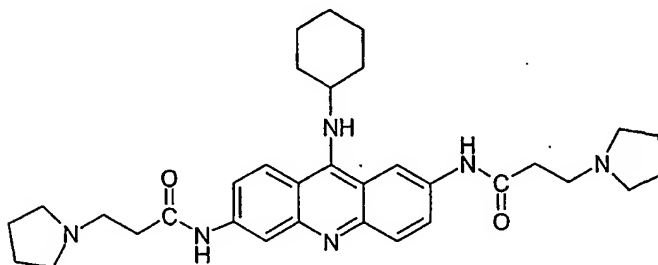
Tetrahydrochloride Salt
(**SB-ACI-20**)

The tetrahydrochloride addition salt, **SB-ACI-20**, of the compound in the previous
20 example, was also prepared by treatment with HCl.

- 142 -

Example 135

N-[9-(Cyclohexylamino)]-2,6-bis(3-pyrrolidinopropionamido)acridine
(**BSU-SB-36/200**)



- 5 2,6-Bisamido-9-chloroacridine **AR-ACO-10** (500 mg, 1.0 mmol) was treated with cyclohexylamine (0.35 mL) according to the general procedure to give the desired product **BSU-SB-36/200** (230 mg, 41%) as a yellow solid.

- ¹H-NMR (CDCl₃) δ 1.06-1.66 (4 H, m, HNCH(CH₂CH₂)₂CH₂), 1.77 (2 H, m,
10 HNCH(CH₂CH₂)₂CH₂), 1.95 (8 H, m, N(CH₂CH₂)₂), 2.59-2.66 (4 H, m, COCH₂CH₂N), 2.73-2.75 (8 H, m, N(CH₂CH₂)₂), 2.89-2.96 (4 H, m, COCH₂CH₂N), 3.89 (1 H, m, HNCH(CH₂CH₂)₂CH₂), 7.30-7.34 (1 H, m), 7.84-8.05 (4 H, m), 8.83-8.84 (1 H, m), 11.58 (1 H, s, NHCO), 11.60 (1 H, s, NHCO).

15

Example 136

Trihydrochloride Salt
(**SB-ACI-21**)

- The trihydrochloride addition salt, **SB-ACI-21**, of the compound in the previous
20 example was also prepared by treatment with HCl.

- 143 -

Biological DataTaq Polymerase Assay

- 5 All compounds were tested using a *Taq* assay to eliminate broad-spectrum polymerase inhibitors and thus filter out any false positives which might have occurred in the TRAP assay. Thus, preferred compounds are "*Taq*-negative." Compounds were tested as their acid addition salts at various final concentrations (0.1, 0.5, 1, 5, 10, 20 and 50 μ M) in a PCR 50 μ L master mix containing 10 ng
- 10 pCI-neo mammalian expression vector (Promega, Southampton, UK) and forward (GGAGTTCCGCGTTACATAAC) and reverse (GTCTGCTCGAAGCATTAACC) primers (200 nmol) as described in the art (see, e.g., Perry et al., 1998a). The product of approximately 1 kb was visualized on a 2% w/w agarose gel following amplification (30 cycles of 94°C for 1 min, 55°C for 1 min and 72°C for 2.5 min).
- 15 The *Taq* assay was carried out until no *Taq* polymerase inhibition was observed. All compounds were found to be *Taq* negative.

Modified Telomeric Repeat Amplification Protocol (TRAP) Assay

- 20 The ability of compounds to inhibit telomerase in a cell-free assay was assessed with a modified TRAP assay using extracts from exponentially growing A2780 human ovarian carcinoma cells. The TRAP assay was performed in 2 steps:
- (a) telomerase-mediated extension of the forward primer (TS: 5'-AATCCGTCGAGCAGAGTT, Oswel Ltd., Southampton, UK) contained in a
- 25 40 μ L reaction mix comprising TRAP buffer (20 mM Tris-HCl (pH 8.3), 68 mM KCl, 1.5 mM $MgCl_2$, 1 mM EGTA, 0.05% v/v Tween 20), 0.05 μ g bovine serum albumin, 50 μ M of each deoxynucleotide triphosphate, 0.1 μ g TS primer, and 3 μ Ci of [α - 32 P]dCTP (Amersham plc, UK). Protein (40 ng or 20 ng) was then incubated with the reaction mix + agent (acid addition and quaternary dimethiodide salts) at
- 30 final concentrations of up to 50 μ M for 20 min at 25°C. A lysis buffer (no protein) control, heat-inactivated protein control, and 50% protein (20 ng or 10 ng) control were included in each assay; and (b) while heating at 80°C in a PCR block of a thermal cycler (Hybaid, UK) for 5 min to inactivate telomerase activity, 0.1 μ g of

- 144 -

reverse CX primer (3'-AATCCCATTCCCATTCCCATTCCC-5') and 2 Units of *Taq* DNA polymerase ("red hot", Advanced Biotechnologies) were added. A 3-step PCR was then performed: 94°C for 30 s, 50°C for 30 s, and 72°C for 1 min for 31 cycles. Telomerase-extended PCR products in the presence or absence of

5 compounds were then determined either by electrophoretic separation using 8% w/w acrylamide denaturing gels and analysis by phosphorimaging or autoradiography, or by harvesting on Whatman filters (25 mm glass microfibre) and analysis by liquid scintillation counting. The data are summarized in Table 1.

10 Growth Inhibition Assay

Growth inhibition was measured in three human ovarian carcinoma cell lines (A2780, CH1, and SKOV-3) and one human cervix carcinoma cell line (A431) using the sulforhodamine B (SRB) assay. Briefly, between 3000 and 6000 cells were

15 seeded into the wells of 96-well microtiter plates and allowed to attach overnight. Compounds (acid addition and quaternary dimethiodide salts) were dissolved at 500 μ M in water and immediately added to wells in quadruplicate at final concentrations of 0.05, 0.25, 1, 5 and 25 μ M. Following an incubation period of 96 hr, remaining cells were fixed with ice-cold 10% w/v trichloroacetic acid (30 min)

20 and stained with 0.4% SRB in 1% v/v acetic acid (15 min). Mean absorbance at 540 nm for each drug concentration was expressed as a percentage of the control untreated well absorbance, and IC_{50} values (concentration required to inhibit cell growth by 50%) were determined for each agent. The data are summarized in Table 1.

25

Table 1 Telomerase Inhibitory Activity and Cytotoxicity for Salts						
Compound		^{tel} IC_{50} (μ M)	Cytotoxicity - IC_{50} (μ M)			
Class	Ref. No.		A2780	CH1	SKOV-3	A431
2,6,9-ine	JH-ACI-105	0.08	>25	15.8	>25	>25
2,7-one	BR-ACO-10	5.8	>25	>25	>25	
2,7-one	BR-ACO-9	2.8	>25	>25	>25	
2,7-one	JH-ACO-22	1.92	>25	>25	>25	>25
2,7-one	JH-ACO-28	0.66	>25	>25	>25	>25
2,7-one	JM-ACO-07	1.97	>25	>25	>25	>25
2,7-one	JM-ACO-09	1.58	>25	>25	>25	>25

- 145 -

Table 1 Telomerase Inhibitory Activity and Cytotoxicity for Salts						
Compound		^{tel} IC ₅₀ (μ M)	Cytotoxicity - IC ₅₀ (μ M)			
Class	Ref. No.		A2780	CH1	SKOV-3	A431
2,7-one	JM-ACO-12	2.33	>25	>25	>25	>25
3,6,9-ine	BR-ACO-19	0.095	10	10.1	13	15.8
3,6,9-ine	BR-ACO-20	0.06	>25	>25	>25	
3,6,9-ine	JC-ACI-3	0.07				2.5
3,6,9-ine	JC-ACI-4	0.15				2.5
3,6,9-ine	JC-ACI-5	0.1	2.8	0.6	3.2	1.3
3,6,9-ine	JC-ACI-9	0.012	>25	20	>25	20
3,6,9-ine	JH-ACI-101	0.16	1.6	2.3	1.2	2.5
3,6,9-ine	JH-ACI-103	0.14	1.0	3.2	2.0	2.5
3,6,9-ine	JH-ACI-65	0.06	>25	17.0	15.8	>25
3,6,9-ine	JH-ACI-69	0.05	12.6	>25	>25	11.2
3,6,9-ine	JH-ACI-74	0.06	12.6	15.8	>25	12.6
3,6,9-ine	JH-ACI-76	0.02	11.0	10.0	15.8	7.1
3,6,9-ine	JH-ACI-78	0.1	7.9	2	4	2
3,6,9-ine	JH-ACI-82	0.09	12.5	2.8	1.1	2.5
3,6,9-ine	JH-ACI-86	0.14	10	3.2	17.8	10
3,6,9-ine	JH-ACI-88	0.21	3.2	2.8	9.3	3.2
3,6,9-ine	JH-ACI-90	0.04	3.2	1.8	3.4	2.2
3,6,9-ine	JM-ACI-14	0.05	19	>25	>25	>25
3,6,9-ine	SB-ACI-11	0.018	>25	17.0	>25	>25
3,6,9-ine	SB-ACI-12	0.018	>25	>25	>25	25
3,6,9-ine	SB-ACI-13	0.066	>25	>25	>25	>25
3,6,9-ine	SB-ACI-14	0.1	>25	>25	>25	>25
3,6-one	BR-ACO-33	1.9	3	3	5.6	
3,6-one	BR-ACO-34	1.8	>25	>25	>25	
3,6-one	BR-ACO-36	3.3	13	11.8	12	
3,6-one	BR-ACO-37	1.6	11.8	11	10.5	
3,6-one	BR-ACO-39	0.74	>25	>25	>25	
3,6-one	BR-ACO-4	8	>25	>25	>25	
3,6-one	BR-ACO-5	5.9	19	13	21	
3,6-one	BR-ACO-6	4.3	>25	>25	>25	
3,6-one	BR-ACO-7	5.7	>25	>25	>25	
3,6-one	BR-ACO-8	49	>25	>25	>25	
3,6-one	JH-ACO-32	1.77	1.9	2.5	2.5	10

- 146 -

REFERENCES

A number of patents and publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

- Autexier, 1999, "Telomerase as a Possible Target for Anticancer Therapy,"
10 Chemistry & Biology, Nov. 1999, Vol. 6, pp. R299-R303.
- Bogert et al., 1930, Collect. Czech. Chem. Comm., Vol. 2, pp. 383-395.
- Bostock-Smith et al., 1988, "Antitumour Polycyclic Acridines, Part 6," Biochemistry,
Vol. 38, No. 21, pp. 6723-6731.
- Gimenez-Arnau et al., 1998, "Antitumour Polycyclic Acridines, Part 2," Anti-Cancer
15 Drug Design, Vol. 13, pp. 125-143.
- Gimenez-Arnau et al., 1998, "Antitumour Polycyclic Acridines, Part 4," Anti-Cancer
Drug Design, Vol. 13, pp. 431-451.
- Goldberg and Kelly, 1946, J.Chem.Soc., p. 102.
- Goldstein and de Simo, 1927, Helv.Chim.Acta., Vol. 10, p. 604.
- 20 Hagan et al., 1997, "Antitumour Polycyclic Acridines, Part 1," J. Chem. Soc., Perkin
Trans. I, p. 2739.
- Hagan et al., 1998, "Antitumour Polycyclic Acridines, Part 3," J. Chem. Soc., Perkin
Trans. I, p. 915.
- Harrison et al., 1999, "Human Telomerase Inhibition by Substituted Acridine
25 Derivatives," Bioorganic & Medicinal Chemistry Letters, Vol. 9, pp. 2463-
2468.
- Julino et al., 1998, "Antitumour Polycyclic Acridines, Part 5," J. Chem. Soc., Perkin
Trans. I, p. 1677.
- Korolev et al., 1976, J. Gen. Chem. USSR (Engl. Trans.), Vol. 46, pp. 2250-2252.
- 30 Korolev et al., 1977, J. Gen. Chem. USSR (Engl. Trans.), Vol. 47, pp. 2118-2122.
- Matsumura, 1929, Journal, Vol. V, No. N, pp. P-P.
- Neidle et al., 1999, "Telomerase as an Anti-Cancer Target: Current Status and
Future Prospects," Anti-Cancer Drug Design, Vol. 14, pp. 341-347.

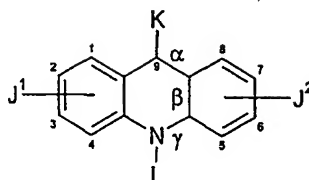
- 147 -

- Perry et al., 1998a, "1,4- and 2,6-Disubstituted Amidoanthracene-9,10-dione Derivatives as Inhibitors of Human Telomerase," J. Med. Chem., Vol. 41, pp. 3253-3260.
- Perry et al., 1998b, "Human Telomerase Inhibition by Regioisomeric Disubstituted Amidoanthracene-9,10-diones," J. Med. Chem., Vol. 41, No. 24, pp. 4873-4884.
- Perry et al., 1998c, "Telomeres and Telomerase: Targets for Cancer Chemotherapy?," Exp. Opin. Ther. Patents, Vol. 8, No. 12, pp. 1567-1586.
- Perry et al., 1999a, "Design, Synthesis and Evaluation of Human Telomerase Inhibitors Based Upon a Tetracyclic Structural Motif," Anti-Cancer Drug Design, Vol. 14, pp. 373-382.
- Perry et al., 1999b, "2,7-Disubstituted Amidofluorenone Derivatives as Inhibitors of Human Telomerase," J. Med. Chem., Vol. 42, No. 14, pp. 2679-2684.
- Read et al., 24 April 2001, "Structure-based design of selective and potent G quadruplex-mediated telomerase inhibitors," PNAS, Vol. 98, No. 9, pp. 4844-4849.
- Sharma et al., 1997, "Preclinical and Clinical Strategies for Development of Telomerase and Telomere Inhibitors," Annals of Oncology, Vol. 8, pp. 1063-1074.
- Sun et al., 1997, "Inhibition of Human Telomerase by a G-Quadruplex-Interactive Compound," J. Med. Chem., Vol. 40, pp. 2113-2116.
- Urquidi et al., 1998, "Telomerase in Cancer: Clinical Applications," Ann. Med., Vol. 30, pp. 419-430.

- 148 -

CLAIMS

1. A compound of the formula:



- 5 wherein either:

(a) K is =O, L is -H, α is a single bond, β is a double bond, γ is a single bond; or,

(b) K is a 9-substituent, L is absent, α is a double bond, β is a single bond, γ is a double bond;

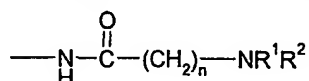
10

and wherein:

J¹ is a 2- or 3-substituent;

J² is a 6- or 7-substituent;

J¹ and J² are each independently a group of the formula:



15

wherein:

n is an integer from 1 to 5; and,

R¹ and R² are independently hydrogen, C₁-₇alkyl, C₃-₂₀heterocyclyl, or C₅-₂₀aryl, or R¹ and R², taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 3 to 8 ring atoms;

20

and wherein, when K is a 9-substituent, K is a group of the formula:



wherein:

25

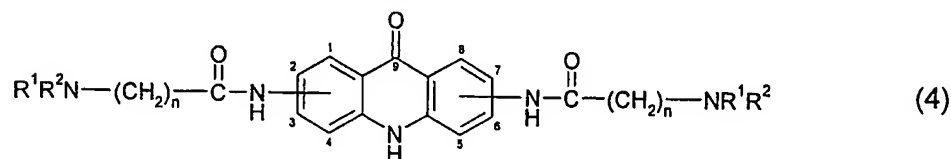
R^N is an amino substituent, and is hydrogen, C₁-₇alkyl, C₃-₂₀heterocyclyl, or C₅-₂₀aryl; and,

Q is C₁-₇alkyl, C₃-₂₀heterocyclyl, or C₅-₂₀aryl, and is optionally substituted;

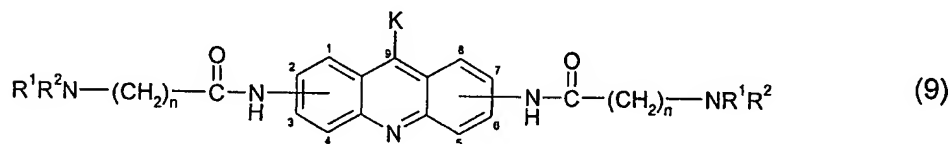
- 149 -

and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

- 5 2. An acridone compound according to claim 1, wherein K is =O, L is -H, α is a single bond, β is a double bond, γ is a single bond, and having the formula:

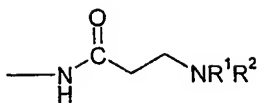


3. An acridine compound according to claim 1, wherein K is a 9-substituent, L is absent, α is a double bond, β is a single bond, γ is a double bond, and having the formula:
- 10



4. A compound according to any one of claims 1 to 3, wherein J¹ is a 2-substituent and J² is a 7-substituent.
- 15 5. A compound according to any one of claims 1 to 3, wherein J¹ is a 3-substituent and J² is a 6-substituent.
6. A compound according to any one of claims 1 to 3, wherein J¹ is a 2-substituent and J² is a 7-substituent.
- 20 7. A compound according to any one of claims 1 to 6, wherein J¹ and J² are the same.
8. A compound according to any one of claims 1 to 7, wherein J¹ and J² are each independently a group of the formula:
- 25

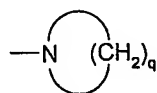
- 150 -



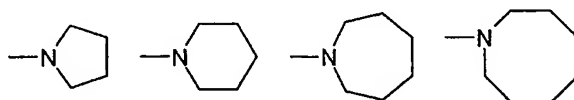
9. A compound according to any one of claims 1 to 8, wherein neither R¹ nor R² is -H.
- 5
10. A compound according to claim 9, wherein R¹ and R² are each independently C₁₋₇alkyl, which is optionally substituted.
11. A compound according to claim 9, wherein R¹ and R² are each independently aliphatic saturated C₁₋₇alkyl, which is optionally substituted.
- 10
12. A compound according to claim 9, wherein R¹ and R² are each independently aliphatic saturated unsubstituted C₁₋₇alkyl.
13. A compound according to claim 9, wherein each -NR¹R² is independently selected from -N(Me)₂, -N(Et)₂, -N(nPr)₂, -N(iPr)₂, -N(nBu)₂, or -N(tBu)₂.
- 15
14. A compound according to any one of claims 1 to 8, wherein R¹ and R², taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 3 to 8 ring atoms, which heterocyclic ring may saturated, partially unsaturated, or fully unsaturated, and is optionally substituted.
- 20
15. A compound according to claim 14, wherein R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring having from 3 to 8 ring atoms, wherein only one of said ring atoms is nitrogen, and all others are carbon, and which heterocyclic ring is optionally substituted.
- 25

- 151 -

16. A compound according to claim 14, wherein R^1 and R^2 , taken together with the nitrogen atom to which they are attached form a cyclic amino group of the following formula, wherein q is an integer from 2 to 7, and wherein said group is optionally substituted:

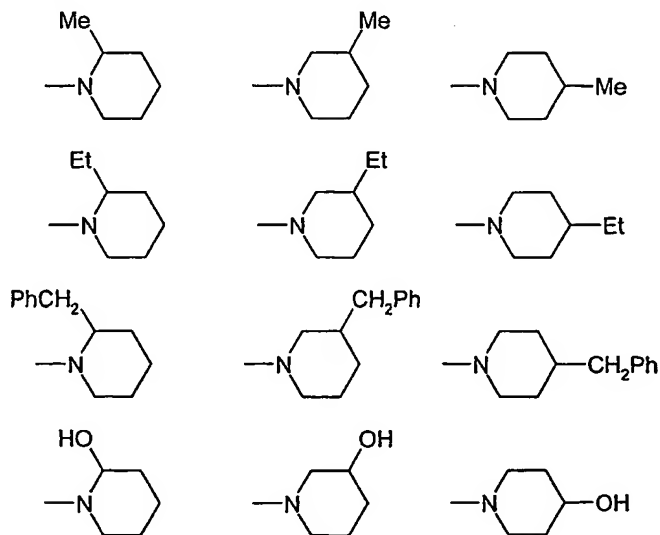


17. A compound according to claim 14, wherein the terminal amino group, $-NR^1R^2$, is one of the following cyclic amino groups, and is optionally substituted:

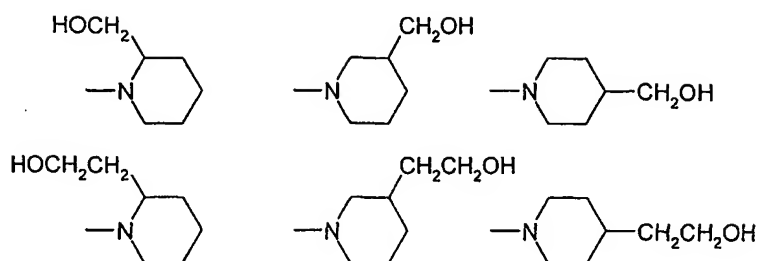


18. A compound according to claim 17, wherein said cyclic amino group is substituted with one or more substituents selected from C_{1-7} alkyl, C_{3-20} aryl- C_{1-7} alkyl, C_{3-20} aryl, C_{1-7} alkyl- C_{3-20} aryl, hydroxy, and C_{1-7} hydroxyalkyl.

19. A compound according to claim 17, wherein each $-NR^1R^2$ is independently selected from:



- 152 -

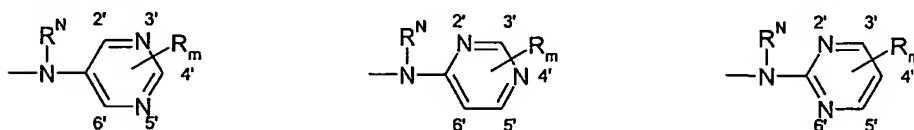


20. A compound according to claim 14, wherein R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated heterocyclic ring having from 3 to 8 ring atoms, wherein said ring has at least two heteroatoms selected from nitrogen, oxygen, and sulfur, which heterocyclic ring is optionally substituted.
21. A compound according to claim 14, wherein the terminal amino group, -NR¹R², is one of the following cyclic amino groups, and is optionally substituted:

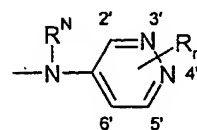
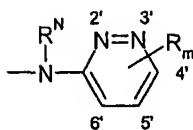
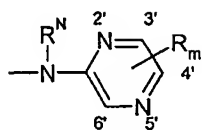


wherein R is hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl.

22. An acridine compound according to any one of claims 1 to 21, wherein R^N is hydrogen or aliphatic saturated C₁₋₇alkyl.
23. An acridine compound according to any one of claims 1 to 22, wherein Q is a C₅₋₂₀aryl group, and is optionally substituted.
24. An acridine compound according to claim 23, wherein K is one of the following:

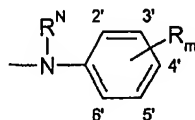


- 153 -



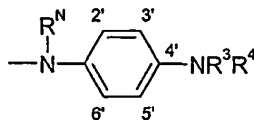
wherein m is an integer from 0 to 3, and each R is independently a substituent.

25. An acridine compound according to any one of claims 1 to 22, wherein K is a group of the formula:



wherein m is an integer from 0 to 5, and each R is independently a substituent.

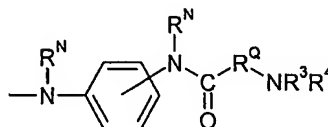
26. An acridine compound according to claim 25, wherein each R is independently selected from: halo, amino, hydroxy, ether, thio, thioether, C₁₋₇alkyl, C₁₋₇haloalkyl, acyl, amido, carboxy, cyano, and aminoalkyl.
27. An acridine compound according to any one of claims 23 to 26, wherein each R is independently a substituent selected from: -F, -Cl, -Br, -I, -OH, -OMe, -OEt, -SH, -SMe, -SEt, -C(=O)Me, -C(=O)OH, -C(=O)OMe, -CONH₂, -CONHMe, -NH₂, -NMe₂, -NEt₂, -N(nPr)₂, -N(iPr)₂, -CN, -NO₂, -Me, -Et, -CF₃, -OCF₃, -CH₂OH, -CH₂CH₂OH, -CH₂NH₂, -CH₂CH₂NH₂, and -Ph.
28. An acridine compound according to claim 27, wherein K is a group of the formula:



wherein -NR³R⁴ is as defined for -NR¹R².

- 154 -

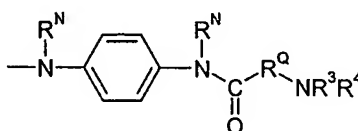
29. An acridine compound according to claim 27, wherein K is a group of the formula:



wherein R^Q is a C_{1-10} alkylene group, and $-NR^3R^4$ is as defined for $-NR^1R^2$.

5

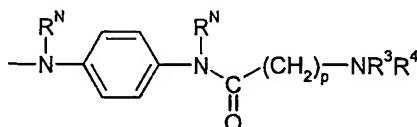
30. An acridine compound according to claim 27, wherein K is a group of the formula:



wherein R^Q is a C_{1-10} alkylene group, and $-NR^3R^4$ is as defined for $-NR^1R^2$.

10

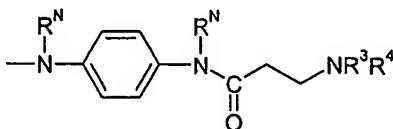
31. An acridine compound according to claim 27, wherein K is a group of the formula:



wherein p is an integer from 1 to 10, and $-NR^3R^4$ is as defined for $-NR^1R^2$.

15

32. An acridine compound according to claim 27, wherein K is a group of the formula:

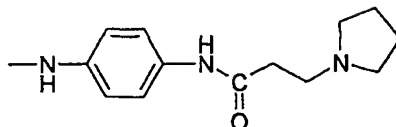


wherein $-NR^3R^4$ is as defined for $-NR^1R^2$.

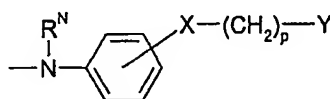
20

- 155 -

33. An acridine compound according to claim 27, wherein K is a group of the formula:



- 5 34. An acridine compound according to claim 27, wherein K is a group of the formula:



wherein:

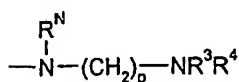
- 10 X is -N(N^R)-, -CH₂-, -O-, or -S-;
 Y is -OH, -OR^Y, or -NR³R⁴;
 R^Y is C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl;
 -NR³R⁴ is as defined above for -NR¹R²; and,
 p is an integer from 1 to 10.

- 15 35. An acridine compound according to any one of claims 1 to 22, wherein Q is an optionally substituted C₁₋₇alkyl group.

36. An acridine compound according to claim 35, wherein Q is an C₁₋₇alkyl group substituted with one or more amino groups, one or more hydroxy groups, or
 20 one or more carboxy groups.

37. An acridine compound according to claim 35, wherein Q is an C₁₋₇alkyl group substituted with one or more amino groups.

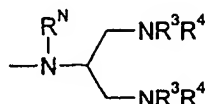
- 25 38. An acridine compound according to claim 37, wherein K is a group of the formula:



wherein p is an integer from 1 to 10, and -NR³R⁴ is as defined for -NR¹R².

- 156 -

39. An acridine compound according to claim 37, wherein K is a group of the formula:

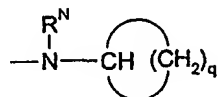


5 wherein $\text{---NR}^3\text{R}^4$ is as defined for $\text{---NR}^1\text{R}^2$.

40. An acridine compound according to any one of claims 1 to 22, wherein Q is, or comprises, an alicyclic saturated C_{1-7} alkyl group, which is optionally substituted.

10

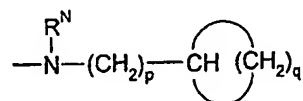
41. An acridine compound according to claim 40, wherein K is a group of the formula:



15

wherein q is an integer from 2 to 7, and wherein the cyclic group is optionally substituted.

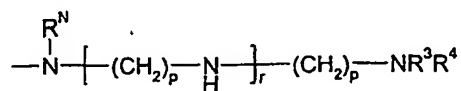
42. An acridine compound according to claim 40, wherein K is a group of the formula:



20

wherein p is an integer from 1 to 10; and q is an integer from 2 to 7, and wherein the cyclic group is optionally substituted.

43. An acridine compound according to any one of claims 1 to 22, wherein K is a group of the formula:



25

wherein p is an integer from 1 to 10, r is an integer from 1 to 4, and $\text{---NR}^3\text{R}^4$ is as defined for $\text{---NR}^1\text{R}^2$.

- 157 -

44. Compound BSU-SB-36/188 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 5 45. Compound BSU-SB-36/190 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
46. Compound BSU-SB-36/194 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 10 47. Compound BSU-SB-36/196 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
48. Compound BSU-SB-36/198 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 15 49. Compound BSU-SB-36/200 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
50. Compound BSU-SB-36/202 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 20 51. Compound JH-ACI-104 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 25 52. Compound AR-ACO-10 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
53. Compound JM-ACI-10 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 30 54. Compound JM-ACI-29 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

- 158 -

55. Compound JM-ACI-31 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 5 56. Compound JM-ACI-33 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
57. Compound JM-ACI-35 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 10 58. Compound JM-ACI-37 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
59. Compound JM-ACI-39 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 15 60. Compound JM-ACI-41 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
61. Compound JM-ACI-45 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 20 62. Compound BR-ACO-16 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 25 63. Compound BR-ACO-17 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
64. Compound JH-ACO-22 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 30 65. Compound JH-ACO-27 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

- 159 -

66. Compound JM-ACO-06 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 5 67. Compound JM-ACO-08 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
68. Compound JM-ACO-11 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 10 69. Compound BR-ACO-21 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
70. Compound BR-ACO-22 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 15 71. Compound BSU-SB-36/152 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
72. Compound BSU-SB-36/158 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 20 73. Compound BSU-SB-36/160 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 25 74. Compound BSU-SB-36/164 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
75. Compound JC-ACI-3A and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 30 76. Compound JC-ACI-4A and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

- 160 -

77. Compound JC-ACI-5A and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 5 78. Compound JC-ACI-9A and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
79. Compound JH-ACI-100 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 10 80. Compound JH-ACI-102 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
81. Compound JH-ACI-64 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 15 82. Compound JH-ACI-68 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 20 83. Compound JH-ACI-73 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
84. Compound JH-ACI-75 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 25 85. Compound JH-ACI-77 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
86. Compound JH-ACI-81 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 30 87. Compound JH-ACI-85 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

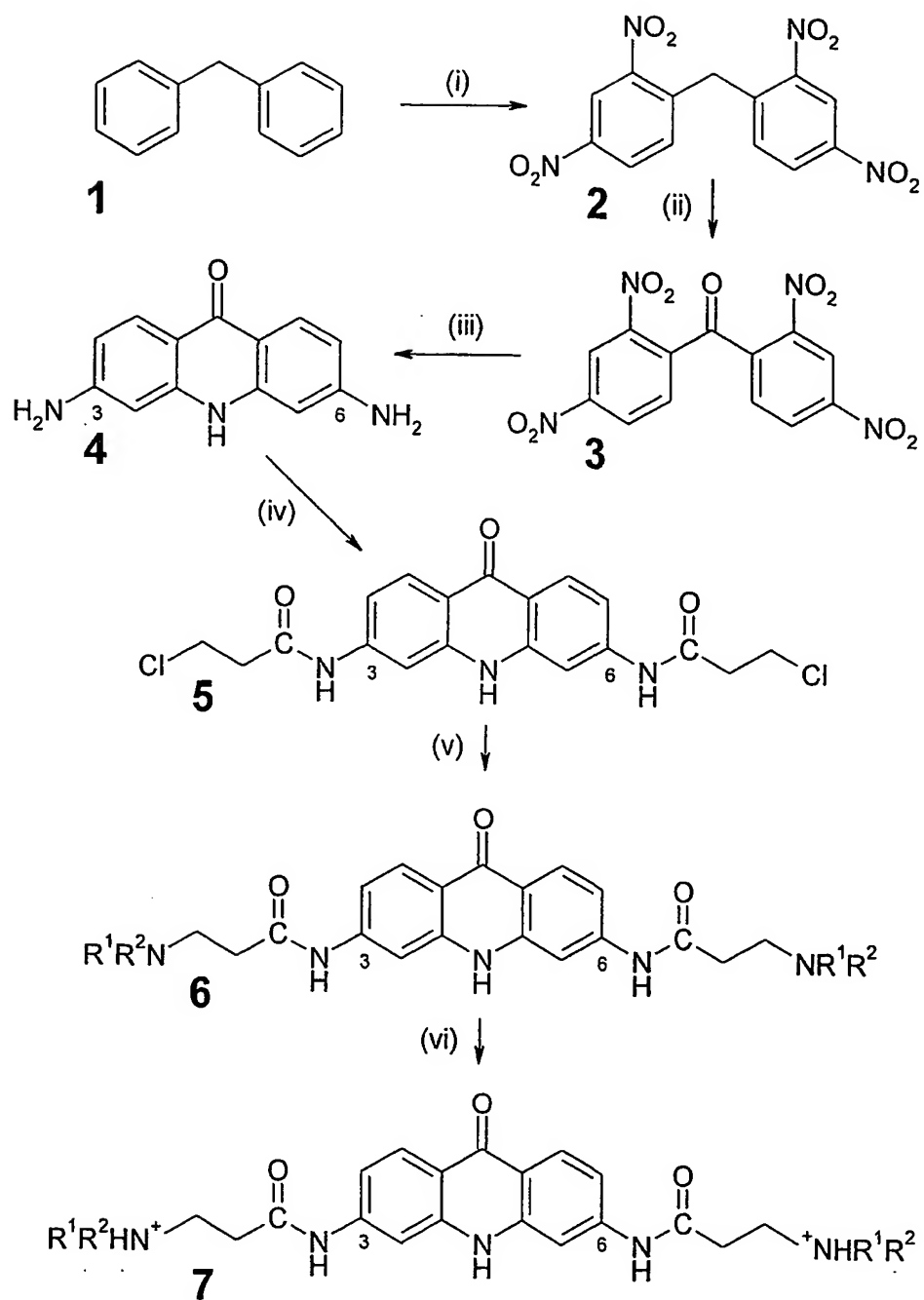
- 161 -

88. Compound JH-ACI-87 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 5 89. Compound JH-ACI-89 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
90. Compound JM-ACI-13 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 10 91. Compound BR-ACO-11 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
92. Compound BR-ACO-12 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 15 93. Compound BR-ACO-13 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
94. Compound BR-ACO-14 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 20 95. Compound BR-ACO-15 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 25 96. Compound BR-ACO-23 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
97. Compound BR-ACO-24 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 30 98. Compound BR-ACO-26 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.

- 162 -

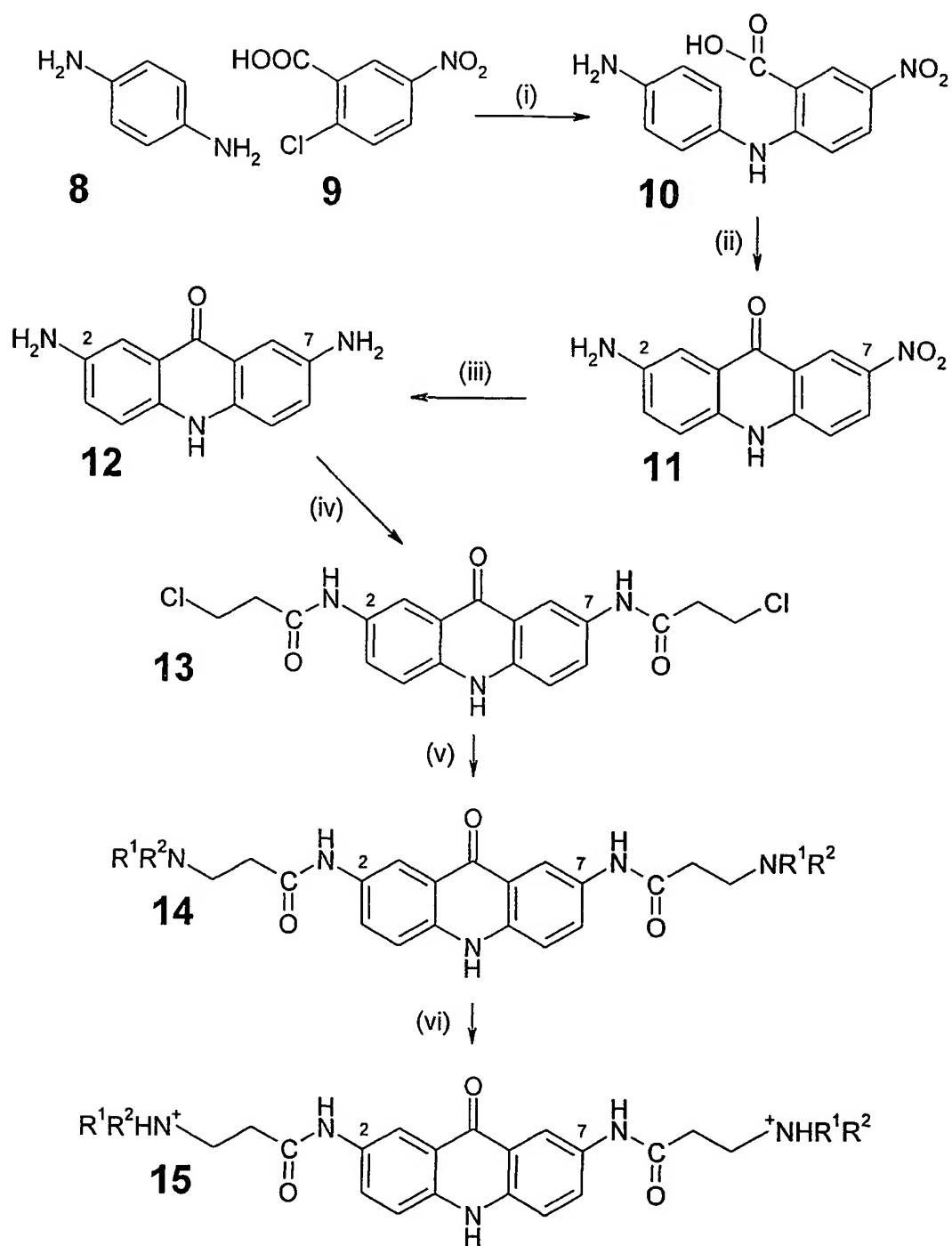
99. Compound BR-ACO-27 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 5 100. Compound BR-ACO-29 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
101. Compound JH-ACO-31 and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof.
- 10 102. A composition comprising a compound according to any one of claims 1 to 101 and a pharmaceutically acceptable carrier or diluent.
- 15 103. A compound according to any one of claims 1 to 101 for use in a method of treatment of the human or animal body.
104. Use of a compound according to any one of claims 1 to 101 for the manufacture of a medicament for use in the treatment of a proliferative condition.
- 20 105. A method of inhibiting telomerase *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of compound according to any one of claims 1 to 101.
- 25 106. A method of regulating cell proliferation *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of compound according to any one of claims 1 to 101.
- 30 107. A method for the treatment of a proliferative condition comprising administering to a subject suffering from said proliferative condition a therapeutically-effective amount of a compound according to any one of claims 1 to 101.

1/7
FIGURE 1



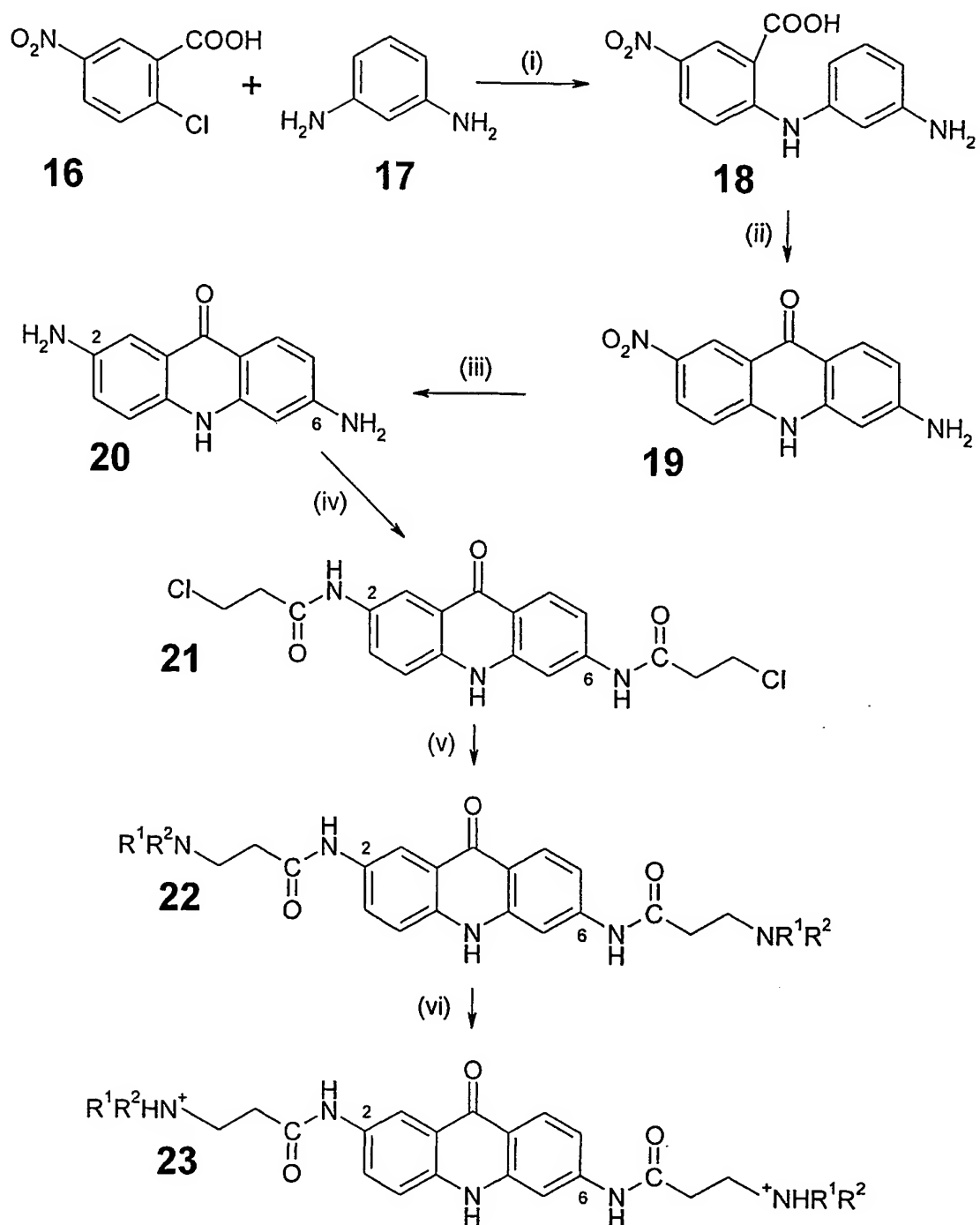
2/7

FIGURE 2



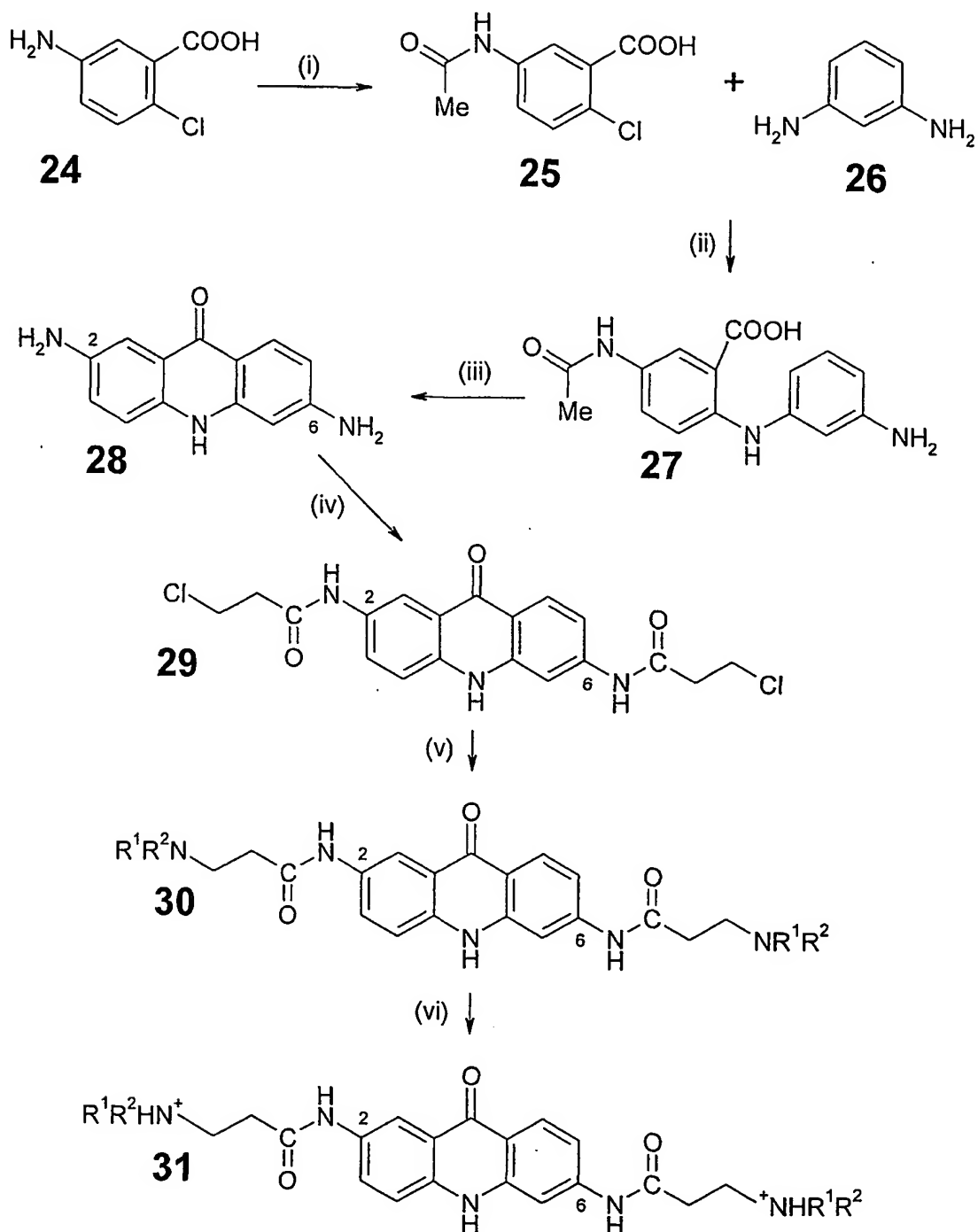
3/7

FIGURE 3A



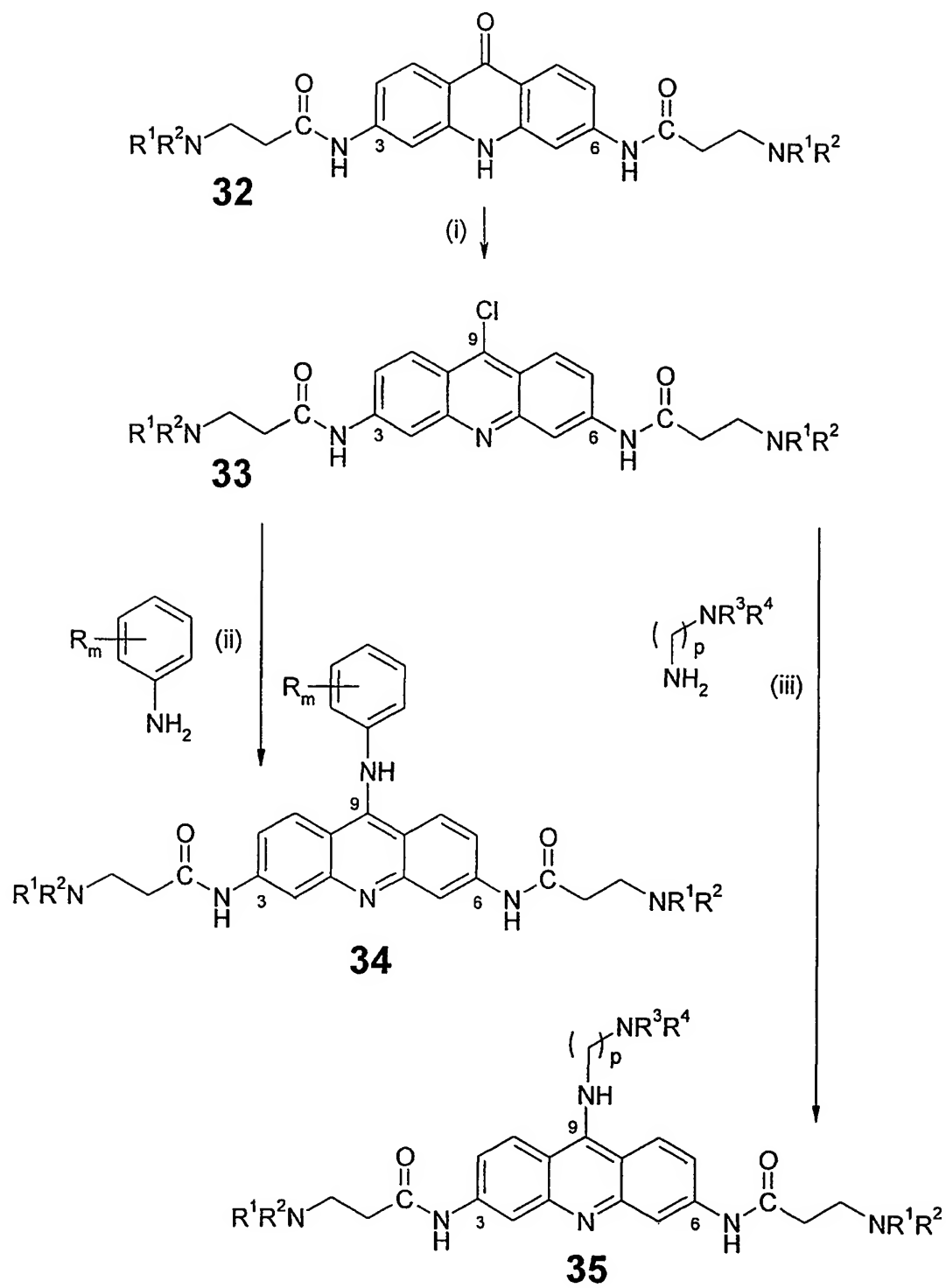
4/7

FIGURE 3B



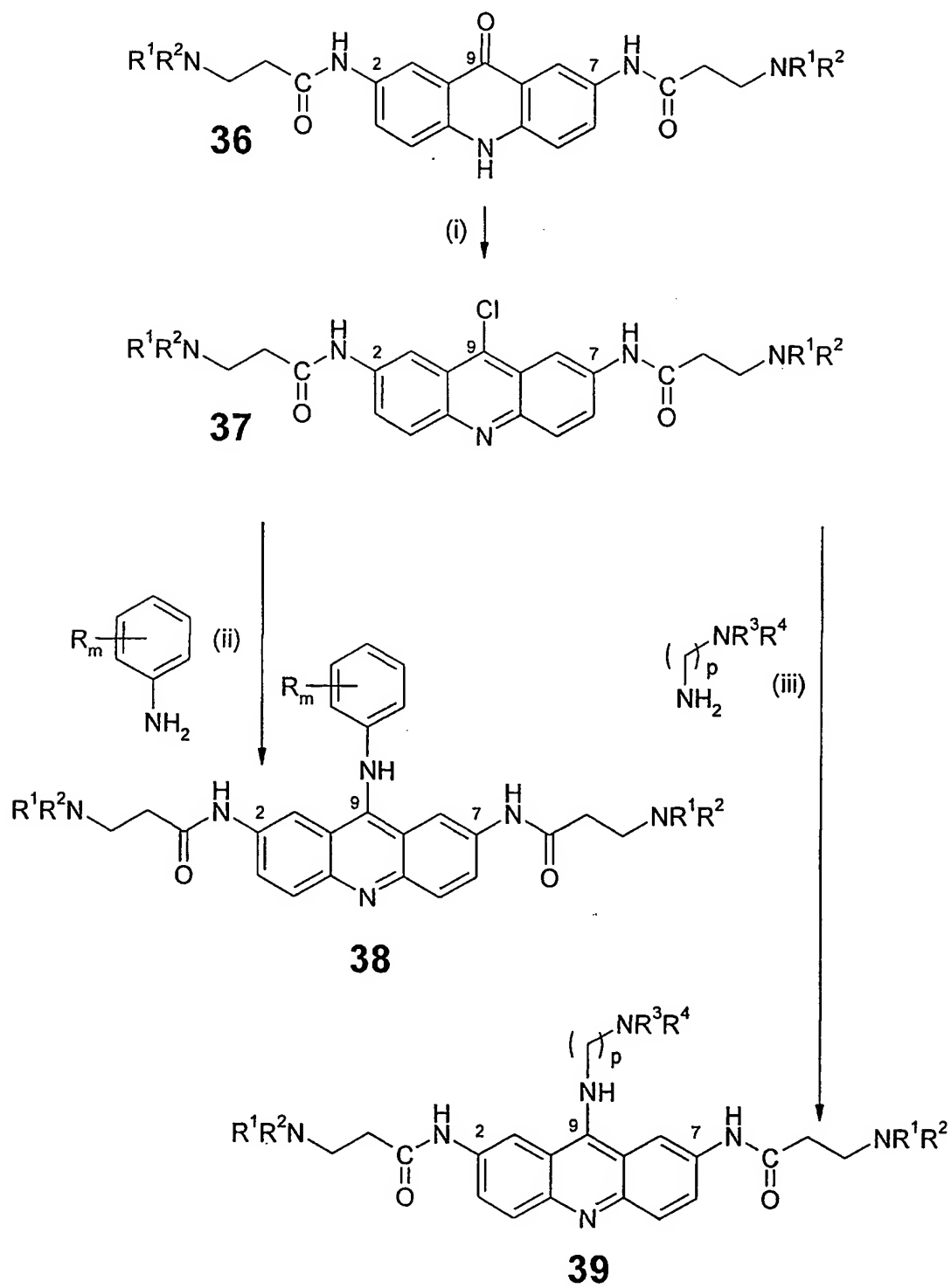
5/7

FIGURE 4

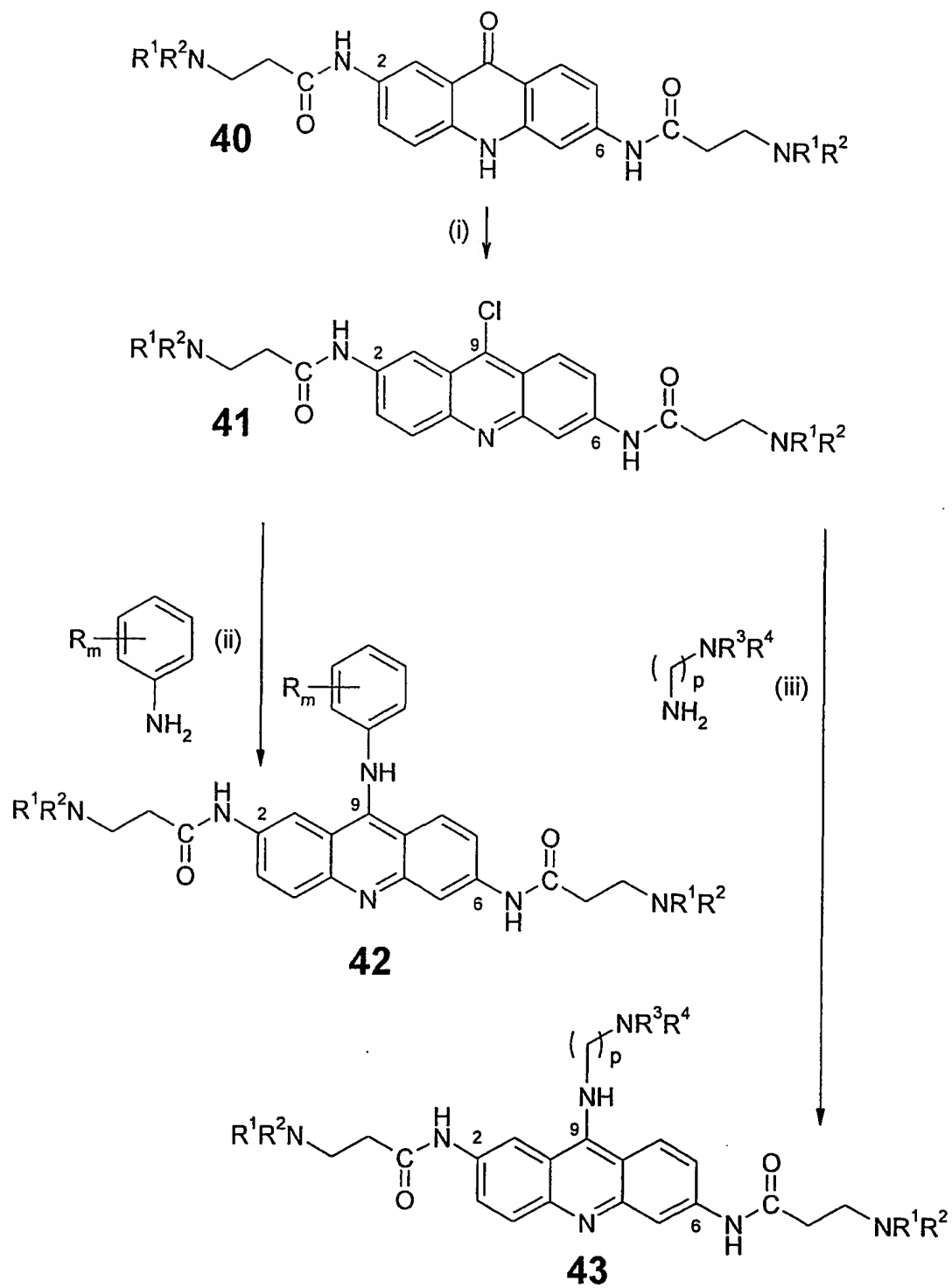


6/7

FIGURE 5



7/7
FIGURE 6



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 January 2002 (31.01.2002)

PCT

(10) International Publication Number
WO 02/008193 A3

(51) International Patent Classification⁷: **C07D 219/06**,
219/08, 219/10, A61K 31/473, A61P 35/00

(21) International Application Number: **PCT/GB01/03046**

(22) International Filing Date: **6 July 2001 (06.07.2001)**

(25) Filing Language: **English**

(26) Publication Language: **English**

(30) Priority Data:
60/216,624 **7 July 2000 (07.07.2000)** **US**

(71) Applicant (for all designated States except US): **CANCER RESEARCH TECHNOLOGY LIMITED** [GB/GB]; 61 Lincoln's Inn Fields, London WC2A 3PX (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NEIDLE, Stephen** [GB/GB]; Rainbow's End, Rainbow Court, Oxhey, Hertfordshire WD1 4RP (GB). **HARRISON, Richard, John** [GB/GB]; 58 Blenheim Gardens, Reading, Berkshire RG1

5QG (GB). KELLAND, Lloyd, Royston [GB/GB]; 123 Hitchings Way, Reigate, Surrey RH2 8EP (GB). **GOWAN, Sharon, Michele** [GB/GB]; 26 Meadway, Tolworth, Surrey KT5 9RG (GB). **READ, Martin** [GB/GB]; 2 Granfield Street, Battersea, London, Greater London SW11 3JH (GB). **RESZKA, Tony** [GB/GB]; 151 Victoria Street, Kilburn, London, Greater London NW6 6DE (GB).

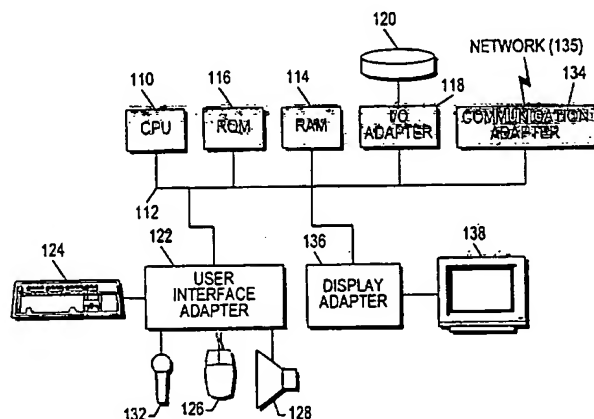
(74) Agents: **ARMITAGE, Ian, A. et al.**; Mewburn Ellis, York House, 23 Kingsway, London, Greater London WC2B 6HP (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,

[Continued on next page]

(54) Title: **THERAPEUTIC ACRIDONE AND ACRIDINE COMPOUNDS**



(57) Abstract: The present invention pertains to acridone and acridine compounds of formula (I), wherein either: (a) K is =O, L is -H, alpha is a single bond, beta is a double bond, gamma is a single bond (acridones); or, (b) K is a 9-substituent, L is absent, alpha is a double bond, beta is a single bond, gamma is a double bond (acridines); and wherein: J¹ is a 2- or 3-substituent; J² is a 6- or 7-substituent; J¹ and J² are each independently a group of the formula -NHCO(CH₂)_nNR¹R², wherein: n is an integer from 1 to 5; and, R¹ and R² are independently hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl, or R¹ and R², taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 3 to 8 ring atoms; and wherein, when K is a 9-substituent, K is a group of the formula -N(R^N)Q, wherein: R^N is an amino substituent and is hydrogen, C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl; and, Q is C₁₋₇alkyl, C₃₋₂₀heterocyclyl, or C₅₋₂₀aryl, and is optionally substituted; and pharmaceutically acceptable salts, esters, amides, solvates, hydrates, and protected forms thereof. The present invention also pertains to pharmaceutical compositions comprising such compounds, and the use of such compounds and compositions, both *in vitro* and *in vivo*, to inhibit telomerase, to regulate cell proliferation, and in the treatment of proliferative conditions, such as cancer.



IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:
2 October 2003

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03046

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D219/06 C07D219/08 C07D219/10 A61K31/473 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HARRISON R J ET AL: "Human Telomerase Inhibition by Substituted Acridine Derivatives" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 17, 6 September 1999 (1999-09-06), pages 2463-2468, XP004188844 ISSN: 0960-894X page 2464, compounds 3 and 4; page 2465, groups (NR2); page 2466, table 1 ---	1-21, 44-107
Y	M A READ ET AL: "Molecular Modeling ..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 42, no. 22, 1999, pages 4538-46, XP000926704 page 4539, compounds 3 to 7 and 10 to 14; page 4540, table 1 --- -/--	1-21, 44-107

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

30 January 2002

Date of mailing of the international search report

19/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/GB 01/03046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DENNY W A ET AL: "Potential antitumor agents. 26. Quantitative relationships between experimental antitumor activity, toxicity, and structure for the general class of 9-anilinoacridine antitumor agents" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 25, no. 3, 1 March 1982 (1982-03-01), pages 276-315, XP002081503 ISSN: 0022-2623 table I	1,22-101
Y	--- G KLOPMAN ET AL: "Computer-Automated ..." MOLECULAR PHARMACOLOGY, vol. 31, no. 4, 1987, pages 457-76, XP000926707 table 1	1,22-101
Y	--- CAIN B F ET AL: "POTENTIAL ANTITUMOR AGENTS. 19. MULTIPLY SUBSTITUTED 4'-(9-ACRIDINYLAMINO)METHANESULFONANILIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 19, no. 9, 1976, pages 1124-1129, XP001041428 ISSN: 0022-2623 table I	1,22-101
Y	--- CAIN B F ET AL: "POTENTIAL ANTITUMOR AGENTS. 17. 9-ANILINO-10-METHYLACRIDINIUM SALTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 19, no. 6, 1976, pages 772-777, XP001041427 ISSN: 0022-2623 table I	1,22-101
Y	--- CAIN B F ET AL: "POTENTIAL ANTITUMOR AGENTS. 14. ACRIDYLMETHANESULFONANILIDES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 17, no. 9, 1974, pages 922-930, XP001041425 ISSN: 0022-2623 table I	1,22-101
Y	--- D J HAGAN ET AL: "Antitumour polycyclic acridines. Part 1. ..." JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANS. 1, 1997, pages 2739-46, XP002188534 cited in the application page 2739, compound 1 ---	1,22-101
	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	M JULINO ET AL: "Antitumour polycyclic acridines. Part 5. ..." JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANS. 1, 1998, pages 1677-84, XP002188535 cited in the application schemes 1, 2	1,22-101
Y	D SUN ET AL: "Inhibition of Human ..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 14, 1997, pages 2113-16, XP002188536 cited in the application page 2113, especially compound 1	1-21, 44-107
Y	P J PERRY ET AL: "1,4- and 2,6-Disubstituted ..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 17, 1998, pages 3253-60, XP002188537 cited in the application page 3254, compounds 15-22; page 3255, table 2	1-21, 44-107
Y	P J PERRY ET AL: "Human Telomerase ..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 24, 1998, pages 4873-84, XP002188538 cited in the application page 4875, scheme 1; page 4876, table 1	1-21, 44-107
A	P J PERRY ET AL: "2,7-Disubstituted ..." JOURNAL OF MEDICINAL CHEMISTRY, vol. 42, no. 14, 1999, pages 2679-84, XP002188539 page 2679, "Introduction" and compound 1	1, 102-107
A	GAMAGE S A ET AL: "SYNTHESIS AND IN VITRO EVALUATION OF 9-ANILINO-3,6-DIAMINOACRIDINES A CTIVE AGAINST A MULTIDRUG-RESISTANT STRAIN OF THE MALARIA PARASITE PLASMODIUM FALCIPARUM" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 10, 1994, pages 1486-1494, XP001041426 ISSN: 0022-2623 table 1	1,102, 103

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MOISAN M ET AL: "NEW ALPHA,OMEGA-DIAMIDO AND ALPHA,OMEGA-DIAMINO MONO-AND BI-BRIDGEDACRIDINE DIMERS" MONATSHFTE FÜR CHEMIE, SPRINGER VERLAG. WIEN, AT, vol. 124, no. 1, 1993, pages 23-35, XP001041424 ISSN: 0026-9247 table 1	1
A	----- S HOFFAMNN ET AL: "Synthese bisbasisch-substituierter ..." ZEITSCHRIFT FÜR CHEMIE, vol. 26, no. 9, 1986, pages 331-2, XP000926708 page 331, compound 2 -----	1